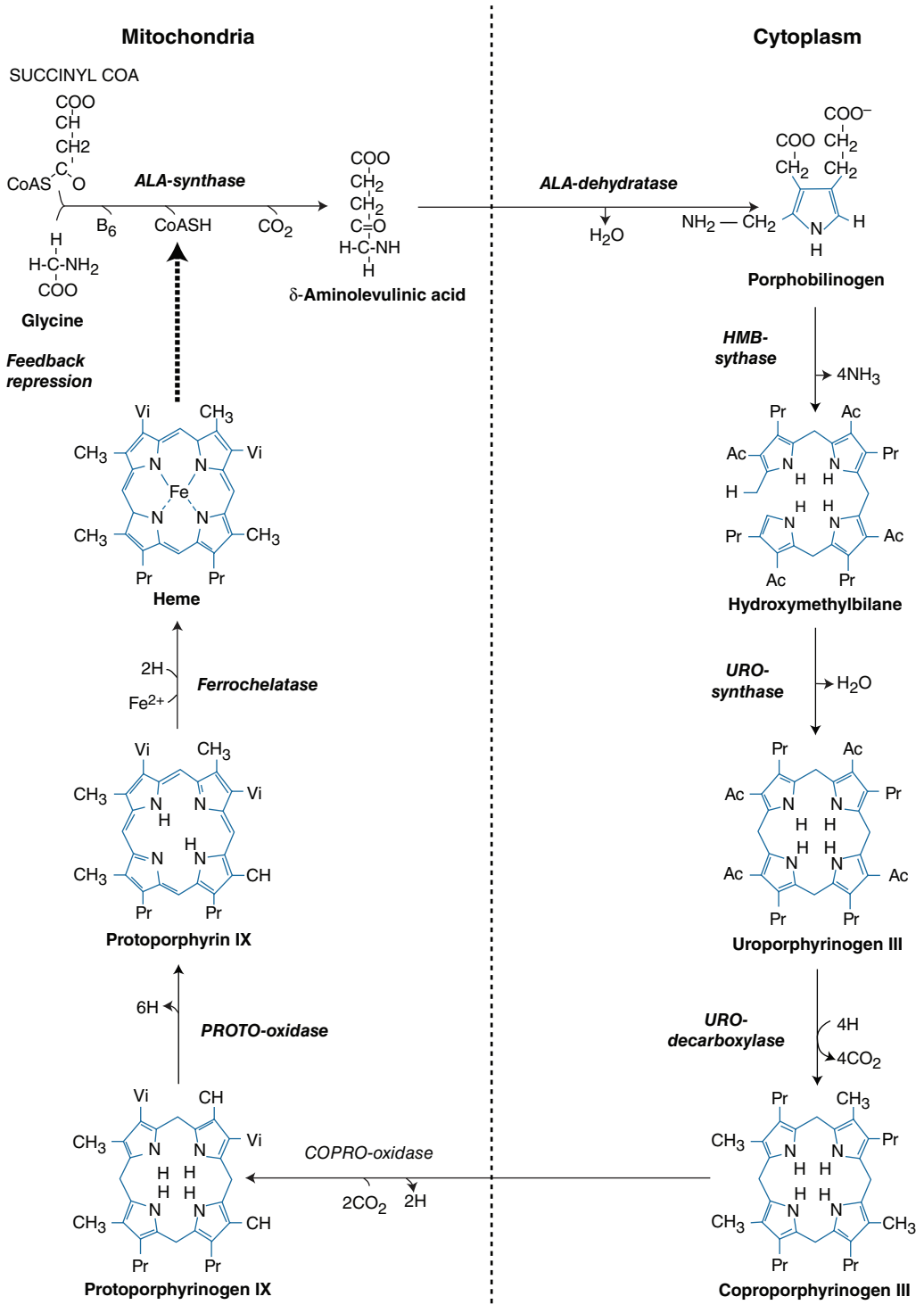

FIGURE 430-2 **The heme biosynthetic pathway showing the eight enzymes and their substrates and products.** Four of the enzymes are localized in the mitochondria and four in the cytosol.

the synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum, and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. As shown in Fig. 430-2, pathway intermediates are the porphyrin precursors, ALA and PBG, and porphyrins (mostly in their reduced forms, known as *porphyrinogens*). At least in humans, these intermediates do not accumulate in significant amounts under normal conditions or have important physiologic functions.

The first enzyme, ALA synthase, catalyzes the condensation of glycine, activated by pyridoxal phosphate and succinyl coenzyme A, to form ALA. In the liver, this rate-limiting enzyme can be induced by a variety of drugs, steroids, and other chemicals. Distinct nonerythroid (e.g., housekeeping) and erythroid-specific forms of ALA synthase are encoded by separate genes located on chromosome 3p21.1 (*ALAS1*) and Xp11.2 (*ALAS2*), respectively. Defects in the erythroid gene *ALAS2* that decrease its activity cause X-linked sideroblastic anemia (XLSA). Recently, gain-of-function mutations in the last exon (11) of *ALAS2* that increase its activity have been shown to cause an X-linked form of EPP, known as *X-linked protoporphyria* (XLP).

The second enzyme, ALA dehydratase, catalyzes the condensation of two molecules of ALA to form PBG. Hydroxymethylbilane synthase (HMB synthase; also known as PBG deaminase) catalyzes the head-to-tail condensation of four PBG molecules by a series of deaminations to form the linear tetrapyrrole, HMB. Uroporphyrinogen III synthase