The CYPs

Cytochrome P450 (CYP450) enzymes are essential for the production of cholesterol, steroids, prostacyclins, and thromboxane A2. They also are necessary for the detoxification of foreign chemicals and the metabolism of drugs. CYP450 enzymes are so named because they are bound to membranes within a cell (cyto) and contain a heme pigment (chrome and P) that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide. There are more than 50 CYP450 enzymes, but the CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 enzymes metabolize 90 percent of drugs. These enzymes are predominantly expressed in the liver, but they also occur in the small intestine (reducing drug bioavailability), lungs, placenta, and kidneys.

The CYPs superfamily of enzymes contain a molecule of heme that is noncovalently bound to the polypeptide chain (Figure 3–2). Many other enzymes that use O_2 as a substrate for their reactions contain heme. Heme is the oxygen-binding moiety, also found in hemoglobin, where it functions in the binding and transport of molecular oxygen from the lung to other tissues. Heme contains one atom of iron in a hydrocarbon cage that functions to bind oxygen in the CYP active site as part of the catalytic cycle of these enzymes. CYPs use O_2, plus H^+ derived from the cofactor-reduced nicotinamide adenine dinucleotide phosphate (NADPH), to carry out the oxidation of substrates. The H^+ is supplied through the enzyme **NADPH-cytochrome P450 oxidoreductase.** Metabolism of a substrate by a CYP consumes one molecule of molecular oxygen and produces an oxidized substrate and a molecule of water as a by-product. However, for most CYPs, depending on the nature of the

substrate, the reaction is "uncoupled," consuming more O_2 than substrate metabolized and producing what is called **activated oxygen** or O_2^-. The O_2^- is usually converted to water by the enzyme superoxide dismutase. Among the diverse reactions carried out by mammalian CYPs are *N*-dealkylation, *O*-dealkylation, aromatic hydroxylation, *N*-oxidation, *S*-oxidation, deamination, and dehalogenation.

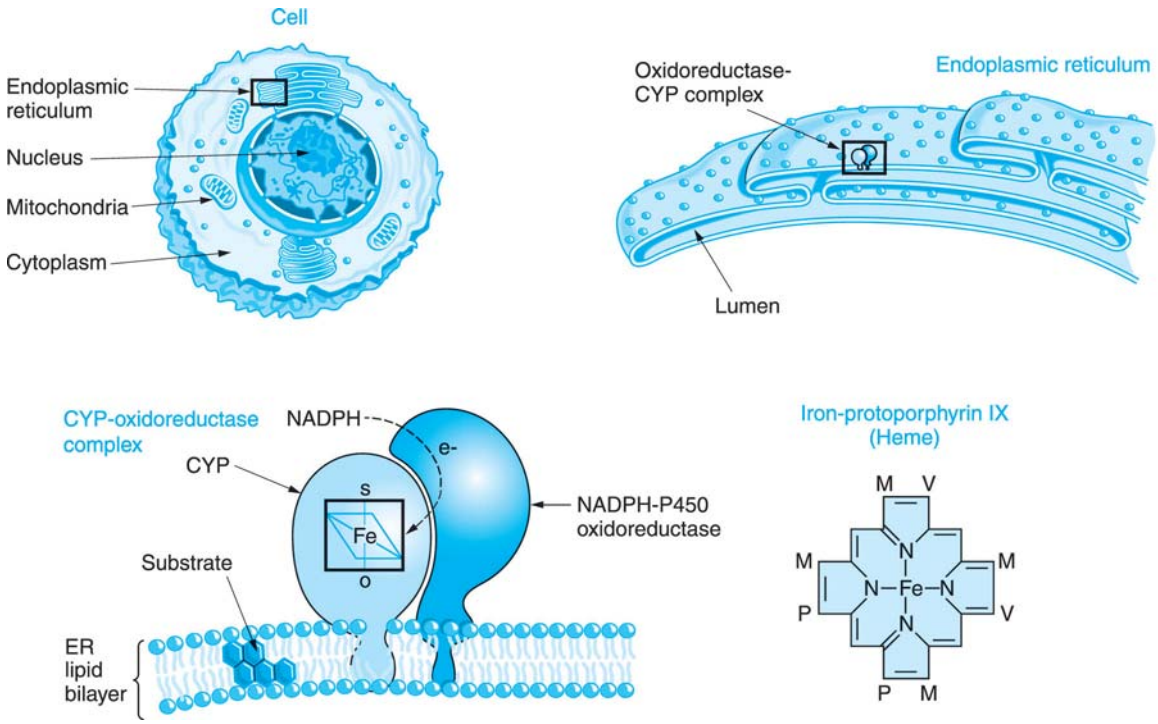

Figure 3–2.
Location of CYPs in the cell.
The figure shows increasingly microscopic levels of detail, sequentially expanding the areas within the black boxes. CYPs are embedded in the phospholipid bilayer of the endoplasmic reticulum (ER). Most of the enzyme is located on the cytosolic surface of the ER. A second enzyme, NADPH-cytochrome P450 oxidoreductase, transfers electrons to the CYP where it can, in the presence of O_2 , oxidize xenobiotic substrates, many of which are hydrophobic and dissolved in the ER. A single NADPH-CYP oxidoreductase species transfers electrons to all CYP isoforms in the ER. Each CYP contains a molecule of iron-protoporphyrin IX that functions to bind and activate O_2 . Substituents on the porphyrin ring are methyl (M), propionyl (P), and vinyl (V) groups.

Drug Interactions

Drugs interact with the CYP450 system in several ways. Drugs may be metabolized by only one CYP450 enzyme (e.g., metoprolol by CYP2D6) or by multiple enzymes (e.g., warfarin [Coumadin] by CYP1A2, CYP2D6, and CYP3A4). Drugs that cause CYP450 metabolic drug interactions are referred to as either **inhibitors or inducers**. Inhibitors block the metabolic activity of one or more CYP450 enzymes. The extent to which an inhibitor affects the metabolism of a drug depends upon **factors** such as the **dose** and the ability of the inhibitor to **bind to the enzyme**. For instance, sertraline (Zoloft) is considered a ***mild inhibitor*** of CYP2D6 at a dose of 50 mg, but if the dose is increased to 200 mg, it becomes a ***potent inhibitor***. Inhibitory effects usually occur immediately. Additionally, a drug can be both metabolized by and inhibit the same enzyme (e.g., erythromycin), or it can be metabolized by one enzyme and inhibit another enzyme (e.g., terbinafine [Lamisil]). Drugs may be intentionally combined to take advantage of CYP450 inhibition. Ritonavir (Norvir), a protease inhibitor and potent CYP3A4 inhibitor, is added to lopinavir (Kaletra) to boost serum levels in patients with human immunodeficiency virus.

Inducers increase CYP450 enzyme activity by increasing enzyme synthesis. Unlike a drug also may be metabolized by the same CYP450 enzyme that it induces.

The following clinical scenario describes a **case of drug interaction**: A 68-year-old white woman taking warfarin, whose condition was previously well controlled on a stable dose, has recently been difficult to anticoagulate to a therapeutic level. Review of her medications reveals the addition of monthly fluconazole (Diflucan) for

recurrent vulvovaginal candidiasis. The physician recognizes the drug interaction between warfarin and fluconazole as a potential cause and switches the patient to an alternate antifungal agent. The patient's International Normalized Ratio quickly stabilizes. As shown in this example, **physicians should be cautious** when prescribing a drug known to be a CYP450 inhibitor or inducer. The **target drug may need to be substituted or the dose adjusted** to account for a potential decrease or increase in metabolism. Information regarding a drug's CYP450 metabolism and its potential for inhibition or induction can be found on the drug label and accessed through the **U.S. Food and Drug Administration (FDA)** or manufacturer's Web sites. The FDA has required this information for every drug approved since 1997.