Editorial

Cytochrome P450 enzymes

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One consequence of the devotion of this journal to drug metabolism and the mechanisms by which drugs interact with each other is that cytochrome P450 enzymes (CYPs) will figure prominently in its contents. This is because CYPs constitute the predominant enzyme system for the metabolism of drugs and are the site of the majority of drug-drug interactions. A series of reviews of current knowledge of the major drug metabolizing CYPs is therefore planned.

CYP genes are found in all species, from bacteria to fungi and from plants to animals. The CYP superfamily presently consists of more than 11,000 genes and the first or ancestral CYP gene probably dates back in evolution to 3.5 billion years ago. CYP proteins are named based on their evolutionary relationship and arranged into families and subfamilies on the basis of percentage amino acid sequence identity. The human genome harbors 57 CYP genes, arranged in 18 families and numerous subfamilies (http://drnelson.uthsc.edu/ CytochromeP450.html). Only three of these families (CYP1, 2 and 3) are involved in the metabolism of drugs and other xenobiotics. In fact, 10 human CYPs from seven subfamilies, namely CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5, are responsible for the metabolism of most drugs. The metabolism of drugs by these subfamilies is of varying importance. According to recent estimates, CYP3A4/5 contributed to the metabolism of 37% of the 200 most frequently prescribed drugs, followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), CYP2C8 (8%), CYP2B6 (4%), CYP2A6 and CYP2E1 (2%) (1). Most other human CYPs are involved in the metabolism of endogenous molecules, including steroids, bile acids, fatty acids, prostaglandins, leukotrienes, vitamin D, biogenic amines and retinoids. CYPs also metabolize nutritional components (e.g., from plants, fungi and food additives) and innumerable environmental pollutants (e.g., polycyclic hydrocarbons, arylamines and herbicides). Most of the drug-metabolizing CYPs also have known or suspected endogenous substrates, such as steroids, bile acids, fatty acids, food components, etc. This may lead to interactions between endogenous physiological and exogenous molecules and also lead to so-called endo-xenobiotic crosstalk (2).

In principle, CYP enzymes can thus metabolize thousands of chemicals. A CYP may have a rather strict catalytic specificity (e.g., in steroid or arachidonic acid metabolism) or be the catalyst for the oxidation of more than 100 drugs (e.g.,

CYP3A4). A hallmark of the substrate specificities of CYPs is that they are "overlapping". One drug may be metabolized by several different CYPs, in spite of the regional- and stereoselectivity of the oxidative reactions occurring, and many different drugs may be metabolized by the same CYP. Recent advances in understanding of the structure-function relationship of the reaction mechanism, helped by the crystal structures of 12 mammalian CYPs, can explain many of the characteristics of these fascinating enzymes.

CYPs are a major source of inter- and intraindividual variation in drug response. Concomitant drug therapy, diet and lifestyle choices (e.g., whether someone smokes or drinks) but also disease (e.g., inflammation) have important effects on the expression of CYP enzymes and cause drug-drug interactions. In particular, members of the CYP1A, CYP2B, CYP2C and CYP3A gene subfamilies are highly inducible by some drugs and xenobiotics. This induction usually is tissuespecific, rapid, dose-dependent, and reversible upon removal of the inducer. The molecular mechanisms by which exogenous and endogenous inducer substances bind to receptors like the cytosolic aromatic hydrocarbon receptor, constitutive androstane receptor and pregnane X receptor, and how this triggers a signaling cascade leading to the increased transcription of CYPs and many other genes (including other drugmetabolizing enzymes and transporters) is now relatively well-known (3).

Since one P450 enzyme may bind many different substrates, competition at the site of drug binding by co-substrates or other chemicals may cause inhibition, which is another source of drug-drug interactions. A certain drug may thus be an inhibitor and an inducer (e.g. ritonavir).

Age, gender, genetic and disease factors can produce additional considerable variability in CYP expression among (and within) individuals. One well-known major source of interindividual variability in drug disposition is genetic polymorphism of CYPs. Many allelic variants exist with most *CYPs*, resulting in genetically-determined pharmacological diversity between individuals (1, 4). A database of human allelic variants of *CYP* genes is freely available on the internet and is continuously updated (http://www.imm.ki.se/CYPalleles/).

Characterization of human drug-metabolizing enzymes and drug transporters has seen major progress in the past few years. As always, however, many questions regarding the function and regulation of CYPs remain unresolved. Of much recent interest are the influence of circadian rhythms (5), of the intestinal microbiome (6), and epigenetic and small RNA regulation of CYPs (7). I am looking forward to the series of articles on CYPs to learn more about all these issues.

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