

Editorial

Cytochrome P450s and their Polymorphic Variants

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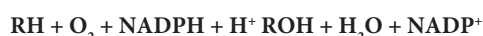
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Received: February 25, 2014; **Accepted:** February 28,
2014; **Published:** March 05, 2014

The cytochrome P450 enzymes (P450s) are a highly conserved family of enzymes present in the cells of all prokaryotes and eukaryotes [1]. P450s are essential to the synthesis of steroids, fatty acids, and some vitamins. P450s are also instrumental in the metabolism of both endogenous and xenobiotic substrates. It is estimated that over 50% of all therapeutics currently in use are biotransformed by the P450 enzyme family [2]. Generally this reaction produces a more-polar, less-toxic, and more readily excretable product. To date, more than 13,000 P450 genes have been identified, and 57 have shown to be present in humans as a result of the Human Genome Project [3]. Furthermore, one quarter of the 57 human P450s play crucial roles in drug metabolism [3].

The P450s are membrane-bound enzymes located in the endoplasmic reticulum or mitochondria of most tissues in mammals [1]. The P450s have been described as “Nature’s most versatile biological catalyst,” because these enzymes catalyze a wide variety of reactions on a structurally diverse assortment of substrates [4]. The most common reactions are mono-oxygenations, such as hydroxylation, epoxidation, *N*- and *O*-dealkylations and nitrogen and sulfur oxidations. Less common reactions include deformylations, dehydrogenations, and reactions that don’t require oxidations, such as reductions and ring expansions [5]. These reactions are considered to be members of the Phase I drug metabolism class of reactions in humans [6]. The following scheme describes the overall stoichiometry for substrate hydroxylation by P450:



The P450s require accessory proteins for successful catalysis. These accessory proteins, known as NADPH-cytochrome P450 reductase (reductase) and, in some cases, cytochrome b5 (b5), are located adjacent to the P450s in the endoplasmic reticulum or mitochondrial membranes. Generally, the P450:reductase:b5 ratio in tissues is 20:1:0.5 [7]. The reductase is essential for electron transfer from the cofactor NADPH to P450 either once or twice during the P450 catalytic cycle, with the first electron always coming from the reductase. The second electron transfer can be completed by either by the reductase or b5; however, b5 involvement in the cycle is known to be dependent on both the P450 and the substrate [8].

In the early 2000’s great advances were made with regards to increasing the expression levels and solubility of microsomal P450s [9]. This enabled crystallization and eventual determination of the three dimensional structures of the P450s. To date, there are over 500 P450 X-ray structures in the Research Collaboratory for Structural

Biology’s Protein Data Bank (RCSB-PDB); approximately 100 of those are human P450s. P450 structures have been obtained in many conformations and for several P450s [10]. Generally, the soluble prokaryotic and the membrane-bound eukaryote P450s have a conserved secondary structure [10]. There are 12 α -helices denoted as A-L, and 4 β -sheets 1-4. Most eukaryotic P450s contain a membrane targeting sequence that anchors the P450s to the cytoplasmic surface of the endoplasmic reticulum or mitochondria. Spatially speaking, the most conserved portions of P450s are helices E, I, J, K, L, and portions of β sheet 1, these form the core of the protein and maintain the binding site for the heme prosthetic group. Substrates bind above the heme surface and are positioned close to the iron-oxo intermediate for oxidations. The outer surface of the substrate binding cavity varies depending on the P450; creating different sizes, shapes, and chemical features which allow for substrate selectivity of the enzymes [11].

Genetic mutations have been described for all genes that encode the human P450s [12]. Population frequencies for the mutations differ and are associated with ethnic groups [12]. The functional significance of the mutation also differs and will, most likely, be dependent on the substrate of interest. In general, the polymorphisms alter either the expression level and/or the catalytic efficiency of the enzyme. These characteristics of the polymorphisms can lead to significant inter-individual variability in P450 activity, which is most clearly exemplified by the dramatic variations in patient responses to drug therapy [13]. Polymorphic forms of P450s contribute to a significant amount of adverse drug reactions [14]. It is estimated that ~86% of the drugs cited in adverse drug reaction studies are metabolized by the polymorphic phase I enzymes [15]. Additionally, costs associated with treating patients who express variant alleles of the P450s are generally significantly greater than costs associated with treating patients expressing the wild type P450 [16]. Currently, many studies are focused on correlating the genotype of the human P450s with the phenotypic outcome of drug response. It has been suggested that enhancing the knowledge of the role of polymorphic P450s in drug metabolism could result in a 10-20% improvement in clinical efficacy and reduce adverse drug reactions by 10-15% [12]. Overall, a better understanding of the mechanism responsible for observed phenotypic variations is necessary for safer and more efficacious drug therapy regimens.

The P450s are essential for the metabolism of the majority of therapeutics used today. Factors that can influence P450 activity, like accessory protein interaction, environmental, structural and/or expression variations, will affect therapeutic outcomes in patients. In order to treat patients in a more personalized manner, future investigations should focus on identifying and describing these factors, then implementing this basic knowledge for the improvement of current therapies in patients.

References

1. Guengerich FP. Cytochrome P450 Enzymes. American Scientist. 1993 ; 81: 440-447.

2. Rendic S. Summary of information on human CYP enzymes: human P450 metabolism data. *Drug Metab Rev.* 2002; 34: 83-448.
3. Rendic S & Guengerich FP. Update information on drug metabolism systems--2009, part II: summary of information on the effects of diseases and environmental factors on human cytochrome P450 (CYP) enzymes and transporters. *Curr Drug Metab.* 2010; 11: 4-84.
4. Estabrook RW. A passion for P450s (remembrances of the early history of research on cytochrome P450). *Drug Metab Dispos.* 2003; 31: 1461-1473.
5. Guengerich FP. Common and uncommon cytochrome P450 reactions related to metabolism and chemical toxicity. *Chem Res Toxicol.* 2001; 14: 611-650.
6. Guengerich FP & Rendic S. Update information on drug metabolism systems--2009, part I. *Curr Drug Metab.* 2010; 11: 1-3.
7. Backes WL & Kelley RW. Organization of multiple cytochrome P450s with NADPH-cytochrome P450 reductase in membranes. *Pharmacol Ther.* 2003; 98: 221-233.
8. Schenkman JB, Jansson I. The many roles of cytochrome b5. *Pharmacol Ther.* 2003; 97: 139-152.
9. Johnson EF, Stout CD. Structural diversity of human xenobiotic-metabolizing cytochrome P450 monooxygenases. *Biochem Biophys Res Commun.* 2005; 338: 331-336.
10. Halpert JR. Structure and function of cytochromes P450 2B: from mechanism-based inactivators to X-ray crystal structures and back. *Drug Metab Dispos.* 2011; 39: 1113-1121.
11. Poulos TL and Johnson EF. Structure of cytochrome P450 enzymes. In P. R. Ortiz de Montellano (Ed.), *Cytochrome P450: Structure, Mechanism and Biochemistry.* 2005; 3: 87-111.
12. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol Sci.* 2004; 25: 193-200.
13. van der Weide J, Hinrichs JW. The influence of cytochrome P450 pharmacogenetics on disposition of common antidepressant and antipsychotic medications. *Clin Biochem Rev.* 2006; 27: 17-25.
14. Evrard A, Mbatchi L. Genetic polymorphisms of drug metabolizing enzymes and transporters: the long way from bench to bedside. *Curr Top Med Chem.* 2012; 12: 1720-1729.
15. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA.* 2001; 286: 2270-2279.
16. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med.* 2001; 7: 201-204.