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Mammalian flavin-containing monooxygenases: structure/function, genetic polymorphisms and role in drug metabolism

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Abstract

Flavin-containing monooxygenase (FMO) oxygenates drugs and xenobiotics containing a "soft-nucleophile", usually nitrogen or sulfur. FMO, like cytochrome *P*450 (CYP), is a monooxygenase, utilizing the reducing equivalents of NADPH to reduce 1 atom of molecular oxygen to water, while the other atom is used to oxidize the substrate. FMO and CYP also exhibit similar tissue and cellular location, molecular weight, substrate specificity, and exist as multiple enzymes under developmental control. The human FMO functional gene family is much smaller (5 families each with a single member) than CYP. FMO does not require a reductase to transfer electrons from NADPH and the catalytic cycle of the 2 monooxygenases is strikingly different. Another distinction is the lack of induction of FMOs by xenobiotics.

In general, CYP is the major contributor to oxidative xenobiotic metabolism. However, FMO activity may be of significance in a number of cases and should not be overlooked. FMO and CYP have overlapping substrate specificities, but often yield distinct metabolites with potentially significant toxicological/pharmacological consequences.

The physiological function(s) of FMO are poorly understood. Three of the 5 expressed human FMO genes, FMO1, FMO2 and FMO3, exhibit genetic polymorphisms. The most studied of these is FMO3 (adult human liver) in which mutant alleles contribute to the disease known as trimethylaminuria. The consequences of these FMO genetic polymorphisms in drug metabolism and human health are areas of research requiring further exploration.

Keywords: Flavin monooxygenase; Drug metabolism; FMO

Abbreviations: BVMOs, Baeyer–Villiger monooxygenases; CYP, cytochrome *P*450; DBM, dinucleotide-binding motif; FADPNR, FAD-dependent pyridine nucleotide reductase PRINTS signature; FMO, flavin-containing monooxygenase; FMOXYGENASE, FMO PRINTS signature; GR, glutathione reductase; PAMO, phenylacetone monooxygenase; PNDRDTASEI, pyridine nucleotide disulfide reductase class-I PRINTS signature; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; TMAU, trimethylaminuria

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1. Introduction

Mammalian flavin-containing monooxygenase (FMO, EC 1.14.13.8) was first described by Dr. Daniel Ziegler and colleagues at the University of Texas at Austin (reviewed in Ziegler, 1980, 1988, 1991, 1993, 2002; Poulsen & Ziegler, 1995). This hepatic microsomal enzyme system was demonstrated to utilize oxygen and NADPH to convert *N*,*N*′-dimethylaniline to the N-oxide (Ziegler & Pettit, 1964; Mitchell & Zieger, 1969). The location, co-factor requirement and activity of FMO toward xenobiotics were very similar to the then recently characterized cytochrome *P*450 (CYP) monooxygenase and for a time this enzyme was known as "Ziegler's enzyme". In 1971, the enzyme was purified from porcine liver microsomes and definitively demonstrated to be a distinct monooxygenase containing flavin, with no heme (Ziegler et al., 1971a; Ziegler & Mitchell, 1972; Ziegler & Poulsen, 1978). Again, based on studies on the catalytic activity of this enzyme, it was referred to as "mixed-function amine oxidase", a term that did not capture its wide substrate range.

FMO is a flavoprotein containing a single FAD. Much of the early work describing the structure/function, mechanism, regulation, and substrate specificity of FMO was with the purified porcine liver enzyme, again led by Dr. Dan Ziegler and his colleague Dr. Larry Poulsen (Ziegler et al., 1971a, 1971b, 1992; Poulsen & Ziegler, 1979, 1995). The pig liver enzyme oxygenates a wide range of sulfur- and nitrogen-containing xenobiotics and, in some cases, also oxygenates selenium, iodine, boron, phosphorus and even carbon. An unusual feature of this class of enzymes is that substrate binding has no effect on velocity. In general, any chemical containing a soft nucleophile that gains access to the peroxyflavin intermediate (see Section 2.1 for details) is a potential substrate.

In 1984, the first direct evidence of the existence of multiple forms of FMO was obtained when the enzyme was purified from rabbit lung microsomes independently by 2 laboratories (Williams et al., 1984; Tynes et al., 1985). The "lung" FMO was distinct from the "liver" FMO in having high activity toward primary alkyl amines, restricted substrate specificity related to steric properties, resistance to detergent inhibition and enhanced thermal stability (Williams et al., 1984, 1985, 1990; Tynes & Hodgson, 1985a, 1985b; Tynes et al., 1985, 1986; Poulsen et al., 1986; Nagata et al., 1990; Hodgson & Levi, 1991; Venkatesh et al., 1992). Since those early studies, FMOs have been purified and/or cloned from multiple sources (Table 1). Until recently, it was thought that only 5 genes were expressed in mammals (Hines et al., 1994; Lawton et al., 1994; Cashman, 1995; Phillips et al., 1995). A sixth human gene, *FMO6*, identified by the Sanger Center chromosome 1 sequencing project, was demonstrated to be a psuedogene (Hines et al., 2002). These FMO genes are located in a cluster on the long arm of chromosome 1 (q23–25). The laboratories of Drs. Ian Phillips and Elizabeth Shephard have recently discovered a second FMO gene cluster, located also on chromosome 1. This second cluster in humans contains an additional 5 genes, all of which appear to be pseudogenes. Interestingly, in the mouse, this second gene cluster contains 3 genes which do not appear to be pseudo genes (Hernandez et al., 2004).

As with the CYP monooxygenase system, over the course of evolutionary plant–animal warfare, FMO developed broad substrate specificity at the expense of turnover. Both monooxygenases are capable of oxidizing thousands of plant alkaloids and other natural products as well as the thousands of synthetic therapeutic drugs. The CYP turnover number for most xenobiotics is 1–20 min^{-1} and the number is slightly higher for FMO, i.e., 30–60 min^{-1}. Although active toward many of the same substrates, CYP and FMO often produce distinct metabolites. It is recognized in the drug development field that potential concerns can arise if a drug contains a structural feature capable of being bio-