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Review

Comparison of xenobiotic-metabolising human, porcine, rodent, and piscine cytochrome P450

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ABSTRACT

Cytochrome P450 proteins (CYP450s) are present in most domains of life and play a critical role in the metabolism of endogenous compounds and xenobiotics. The effects of exposure to xenobiotics depend heavily on the expression and activity of drug-metabolizing CYP450s, which is determined by species, genetic background, age, gender, diet, and exposure to environmental pollutants. Numerous reports have investigated the role of different vertebrate CYP450s in xenobiotic metabolism. Model organisms provide powerful experimental tools to investigate Phase I metabolism. The aim of the present review is to compare the existing data on human CYP450 proteins (1–3 families) with those found in pigs, mice, and fish. We will highlight differences and similarities and identify research gaps which need to be addressed in order to use these species as models that mimic human traits. Moreover, we will discuss the roles of nuclear receptors in the cellular regulation of CYP450 expression in select organisms.

Contents

Abbreviations: BaP, benzo[a]pyrene; BFCOD, benzyloxy-4-trifluoromethylcoumarin O-debenzylase; CAR, constitutive androstane receptor; CYP, cytochrome P450; EROD-7, ethoxyresorufin dealkylation; GR, glucocorticoid receptor; HAHs, halogenated aromatic hydrocarbons; HBCD, hexabromocyclododecane; HNF, hepatocyte nuclear factor; MROD-7, methoxyresorufin O-demethylation; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; PXR, pregnane X receptor; RXRα, Retinoid X receptor alpha; VDR, vitamin D receptor.

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1. Introduction

Cytochromes (CYPs) P450 are membrane-bound enzymes with widespread and diverse functions. For nearly 60 years, researchers have identified CYP-encoding genes and verified protein expression. These data confirm the presence of CYPs in many organisms, including plants, fungi, and bacteria. More than 21,000 distinct CYP proteins are currently known (Nelson, 2009). CYPs are conveniently arranged into families and subfamilies based on the degree of similarity among amino acid sequences. In humans, pigs, mice, and fish, 18 families of CYPs were identified; CYP1–CYP5, CYP7, CYP8, CYP11, CYP17, CYP19, CYP20, CYP21, CYP24, CYP26, CYP27, CYP39 (not detected in fugu fish (Nelson, 2003)), CYP46, and CYP51 (Goldstone et al., 2010). It is estimated that the human, pig, mouse, and fish genomes contain 57 (Hasler et al., 1999), 54 (Nelson, 2009), 102 (Nelson et al., 2004), and 137 (Uno et al., 2012) genes, respectively. The number of CYP genes varies not only between (Nelson 2003; Nelson et al., 2004) but also within species (Gibbs et al., 2004). For example, it has been identified 61 CYP genes in channel catfish, *Ictalurus punctatus* (Zhang et al., 2014) and 94 in zebrafish, *Danio rerio* (Goldstone et al., 2010). In rodents, 4 *Cyp2j* genes in rat and 8 in mice (Gibbs et al., 2004). The CYP2 K subfamily

Table 1
Classification of human, porcine, murine and piscine CYP enzymes.

Family	Subfamily	Human	Pig	Mouse	Fish	Note
CYP1	A	1A1	1A1	1a1	1A	
		1A2	1A2	1a2		
	B	1B1		1b1	1B1	
					1B2	identified in *Cyprinus caprio*
	C				1C1	identified in *Fugu rubripes*, *Danio rerio*, *Anguilla japonica,* and *Cyprinus caprio*
					1C2	
	D				1D	identified in *Danio rerio*
CYP2	A	2A6	2A19	2a4		The CYP2 family also contains 2F, 2G, 2J, 2 K, 2N, 2P, 2R, 2S, 2U, 2W, 2X, 2Y, and 2Z subfamilies; however, they are not involved in drug metabolism
		2A7		2a5		
		2A13		2a12		
				2a22		
	B	2B6	2B22	2b9	2B	
		2B7		2b10		
				2b13		
				2b19		
				2b23		
	C	2C8	2C32	2c29		
		2C9/10	2C33	2c37		
		2C18	2C34	2c38		
		2C19	2C35	2c39		
			2C36	2c40		
			2C42	2c44		
			2C49	2c50		
			2C91	2c54		
				2c55		
				2c65		
				2c66		
				2c67		
				2c68		
				2c69		
				2c70		
	D	2D6	2D21	2d9		
		2D7	2D25	2d10		
		2D8		2d11		
				2d12		
				2d13		
				2d22		
				2d26		
				2d34		
				2d40		
	E	2E1	2E1	2e1	2E1-like	
CYP3	A	3A3/4	3A22	3a11	3A-like	Fugu fish have a CYP3 B subfamily (3B1 and 3B2). Ray-finned fish have CYP3A, CYP3B, CYP3C and CYP3D
		3A5	3A29	3a13	3A27	
		3A7	3A39	3a16	3A30	
		3A43	3A46	3a25	3A37	
				3a41	3A38	
				3a44	3A48	
				3a57	3A49	
				3a59	3A50	
					3A56	
					3A65	
					3A86	
					3A87	
					3A136	
					3A138	

Human, porcine, murine, and piscine CYP enzymes are taken from Nelson (2009) and Yan and Cai (2010).