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Review

Cytochrome P450 (CYP) in fish

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ABSTRACT

Cytochrome P450 (CYP) enzymes are members of the hemoprotein superfamily, and are involved in the mono-oxygenation reactions of a wide range of endogenous and exogenous compounds in mammals and plants. Characterization of CYP genes in fish has been carried out intensively over the last 20 years. In Japanese pufferfish (*Takifugu rubripes*), 54 genes encoding P450s have been identified. Across all species of fish, 137 genes encoding P450s have been identified. These genes are classified into 18 CYP families: namely, CYP1, CYP2, CYP3, CYP4, CYP5, CYP7, CYP8, CYP11, CYP17, CYP19, CYP20, CYP21, CYP24, CYP26, CYP27, CYP39, CYP46 and CYP51.We pinpointed eight CYP families: namely, CYP1, CYP2, CYP3, CYP4, CYP11, CYP17, CYP19 and CYP26 in this review because these CYP families are studied in detail. Studies of fish P450s have provided insights into the regulation of P450 genes by environmental stresses including water pollution. In this review, we present an overview of the CYP families in fish.

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1. Introduction

The CYP gene superfamily consists of a large number of genes encoding P450 enzymes, which typically catalyze monooxygenase reactions involving molecular oxygen and an equivalent number of electrons. The enzymes are involved in the detoxification of exogenous chemicals such as drugs, chemical carcinogens, and environmental pollutants, and in the metabolism of endogenous substrates, such as steroids, fatty acids, vitamins, and prostanoids (Nebert et al., 2004).

Large amounts of pollutants, including pharmaceuticals used in human and veterinary medicine, are released into the environment from human activities. These pollutants are eventually dispersed in the aquatic environment through various routes, such as atmospheric deposition, direct discharge, land run-off, and food-chain transfer. Numerous studies of the CYP1A isoform in fish have demonstrated its utility as a biomarker for aquatic pollution (Fent, 2003; Moore et al., 2003; Williams et al., 1998). For example, CYP1A1-dependent ethoxyresorufin O-deethylase (EROD) activity is used as an indicator of environmental contamination by polycyclic aromatic hydrocarbons and dioxins (Orrego et al., 2005; Parente et al., 2008; Schlezinger and Stegeman, 2001). Thus, the study of fish P450 contributes to the monitoring of environmental chemicals, as well as increasing our understanding of marine biology.

In the late 1980s, the presence of CYP was shown in the livers of rainbow trout and other fishes (Heilmann et al., 1988; Melancon et al., 1981; Stegeman, 1989; Winkelhake et al., 1983; Winston et al., 1988). Multiple forms of CYPs have been detected, predominantly in the liver. CYP genes have been cloned, and characterized from numerous freshwater and marine fish. Analysis of the Japanese pufferfish (or Fugu) genome has revealed 54 CYP genes (Nelson, 2003). Currently, 18 CYP gene families, CYP1, CYP2, CYP3, CYP4, CYP5, CYP7, CYP8, CYP11, CYP17, CYP19, CYP20, CYP21, CYP24, CYP26, CYP27, CYP39, CYP46 and CYP51 have been identified in fish (Table 1) [http://www.bioscience.org/guides/format.pdf] (Nelson, 2003).

1.1. *CYP1 family*

In fish, the CYP1 family consists of four subfamilies, CYP1A, CYP1B, CYP1C and CYP1D. CYP1A gene products catalyze the oxidation of environmental carcinogens, and are therefore critical determinants in pathways leading either to detoxification and excretion or to DNA adduct formation and carcinogenesis (Gelboin, 1980). In fish, CYP1A subfamily plays important roles in the metabolism and activation of carcinogenesis and is used as a biomarker to assess contamination of the aquatic environment (Brammell et al., 2010; Goksoyr, 1995; Jung et al., 2011; Nilsen et al., 1998). cDNAs encoding CYP1A enzymes have been isolated from various fish species such as rainbow trout (*Oncorhynchys mykiss*) (Rabergh et al., 2000), mummichog (*Fundulus heteroclitus*) (Morrison et al., 1998), European sea bass (*Dicentrarchus labrax*) (Stien et al., 1998), Atlantic salmon (*Salmo salar*) (Arukwe, 2002), medaka (*Oryzias latipes*) (Kim et al., 2004), yellow catfish (*Pelteobagrus fulvidraco*) (Kim et al., 2008a), crucian carp *(hybridized Prussian carp*) (Fu et al., 2011) and hermaphroditic fish, mangrove killifish (*Rivulus marmoratus*) (Lee et al., 2005). The fish CYP1A subfamily of enzymes metabolizes various substrates. Rainbow trout CYP1A catalyzes 7-ethoxyresorufin O-deethylation and ibuprofen 2OH-hydroxylation (Gomez et al., 2011; Levine and Oris, 1999). CYP1A from the liver of feral leaping mullet (*Liza saliens*) shows a high substrate specificity for 7-ethoxyresorufin and methoxyresorufin (Sen and Arinc, 2000). CYP1A is the major enzyme involved in catabolism of pregnenolone in the rainbow trout embryo (Petkam et al., 2003a,b). CYP1A expressed from zebrafish (*Danio rerio*) cDNA metabolizes 7-ethoxyresorufin, estradiol and benzopyrene (Chung et al., 2004; Scornaienchi et al., 2010a,b). *E. coli* transformed with CYP1A9 cDNA from Japanese eel (*Anguilla japonica*) bioconverts estradiol and flavanone (Uno et al., 2008).

Four P450 type 1 family enzymes (CYP1B, CYP1C1, CYP1C2 and CYP1D) have been isolated from diverse fish species. CYP1B1 cDNAs have been isolated from two teleost fish species (scup, *Stenotomus chrysops* (Godard et al., 2000) and European plaice, *Pleuronectes platessa* (Godard et al., 2000)), as well as the common carp (*Cyprinus carpio*) (El-kady et al., 2004). CYP1C cDNAs have been isolated from scup (Godard et al., 2000), the common carp (*Cyprinus carpio*) (Itakura et al., 2005) and mummichog (*F. heteroclitus*) (Wang et al., 2006), and CYP1D cDNAs have been isolated from the three-spined stickleback (*Gasterosteus aculeatus*), killifish, medaka and zebrafish (Goldstone and Stegeman, 2008; Zanette et al., 2009).

Expression of CYP1D1 mRNA is not induced by aryl hydrocarbon receptor agonist (Goldstone et al., 2010; Zanette et al., 2009). CYP1B1, CYP1C1 and CYP1C2 expressed from zebrafish (*D. rerio*) cDNA metabolizes resorufin based-substrate, estradiol and benzopyrene (Scornaienchi et al., 2010a,b). Analysis of amino acid sequence domains suggests that fish CYP1B, CYP1C and CYP1D have unique catalytic functions or substrates; however, the function of these P450s is little known. Further, CYP1C has not been identified in mammals. Therefore, CYP1C may have fish-specific catalytic activities. Lately CYP1D1 gene was identified in monkey and CYP1D1 protein catalyzed ethoxyresorufin O-deethylation and caffeine 8-hydroxylation (Kawai et al., 2010; Uno et al., 2011). Fish CYP1D may metabolize these substrates.

Expression of fish CYP1 family mRNA, like that in mammals, is induced by various compounds such as polychlorinated biphenyls (PCB), beta-naphthoflavone, cobalt, zinc, benzopyrene, pesticides and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Bugiak and Weber, 2009; Calo et al., 2009; Ceyhun et al., 2011, 2012; Chung-Davidson et al., 2004; Jonsson et al., 2007; Kim et al., 2008b; Rabergh et al., 2000; Sanden and Olsvik, 2009; Zanette et al., 2009). In mammals, the expression of the mRNA of CYP1 families is regulated by a cytosolic transcriptional factor, aryl hydrocarbon receptor (Ah receptor) (Beischlag et al., 2008; Gu et al., 2000). Ah receptor has a high affinity to planar compounds, such as dioxins and polyaromatic hydrocarbons (PAHs). In the nucleus, Ah receptor forms a complex with the Ah receptor nuclear translocator (Arnt), which subsequently binds to the xenobiotic response element (XRE, or dioxin response element DRE) in the 5′-upstream region of CYP1A and CYP1B genes. Ah receptor is a member of the basic helix-loop-helix Per-Arnt-Sim (bHLH-PAS) super family of proteins, and is widely distributed in

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