Review Article

CYP4A : บทบาท การแสดงออก และผลกระทบทางคลินิก

ณฐพล กุลเจริญวิรัตน์[1,2], กนกวรรณ จารุกำจร[2,3]*

[1] นักศึกษาปริญญาตรี เภสัชศาสตรบัณฑิต (หลักสูตรนานาชาติ) คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น จังหวัดขอนแก่น 40002
[2] กลุ่มวิจัยฤทธิ์ทางยาของผลิตภัณฑ์ธรรมชาติโดยเทคโนโลยีชีวภาพทางเภสัชศาสตร์ (PANPB) มหาวิทยาลัยขอนแก่น จังหวัดขอนแก่น 40002
[3] รองศาสตราจารย์, สาขาวิชาเภสัชเคมี คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น จ ขอนแก่น.40002
*ติดต่อผู้นิพนธ์: คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น อำเภอเมือง จังหวัดขอนแก่น 40002 โทรศัพท์: 043-202305, โทรสาร: 043-202379, อีเมล์: kanok_ja@kku.ac.th

บทคัดย่อ

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ณฐพล กุลเจริญวิรัตน์[1,2], กนกวรรณ จารุกำจร[2,3]*

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ไซโตโครมพี 450 4 เอ (CYP4A) เป็นเอนไซม์ที่มีบทบาทสำคัญในปฏิกิริยาโอเมก้า/โอเมก้า-1 ไฮดรอกซิเลชัน (ω/ω-1 hydroxylation) ของกรดไขมัน ปฏิกิริยาโอเมก้าไฮดรอกซิเลชันของกรดอะราชิโดนิก (arachidonic acid) ผ่าน CYP4A ได้เป็นกรด 20-ไฮดรอกซีไอโคซาเตตระอีโนอิก (20-hydroxyeicosatetraenoic acid, 20-HETE) ซึ่งเป็นสารที่มีความแรงในการทำให้หลอดเลือดหดตัวที่เกี่ยวข้องกับโรคหลอดเลือดหัวใจ ดังนั้นการควบคุมการแสดงออกของ CYP4A จึงเป็นปัจจัยหนึ่งที่ส่งผลต่อสภาวะดังกล่าว กลไกการควบคุมการแสดงออกของ CYP4A จากการศึกษาในสัตว์ฟันแทะพบว่าเกี่ยวข้องกับตัวรับนิวเคลียร์เพอรอกซิโซมโพรลิเฟอเรเตอร์แอกทิเวเตตรีเซปเตอร์แอลฟา (peroxisome proliferator activated receptor α, PPARα) โดยภายหลังการจับกับลิแกนด์ อาทิ ไฟเบรต (fibrates) พลาสติไซเซอร์ (plasticizers) และสารกำจัดศัตรูพืช จะเกิดเป็นสารประกอบเชิงซ้อนระหว่าง PPARα กับลิแกนด์และเคลื่อนเข้าสู่นิวเคลียสเพื่อจับเป็นเฮเทอโรไดเมอร์กับเรตินอยด์เอ็กซ์รีเซปเตอร์ (retinoid X receptor, RXR) ก่อนเข้าจับกับลำดับเบสเฉพาะเจาะจงบนเพอรอกซิโซมโพรลิเฟอเรเตอร์เรสพอนส์เอลีเมนต์ (peroxisome proliferator response element, PPRE) ของยีน CYP4A แล้วส่งผลกระตุ้นการถอดรหัสของยีน อย่างไรก็ดีกลไกการเหนี่ยวนำโดยสารดังกล่าวไม่เกิดขึ้นใน CYP4A ของมนุษย์ แม้ว่ามนุษย์จะมีร้อยละความคล้ายคลึงของลำดับเบสใน CYP4A ที่สูงเมื่อเปรียบเทียบกับสัตว์ฟันแทะ กลไกการควบคุมการแสดงออกของยีน CYP4A ในมนุษย์จึงยังไม่ชัดเจนในปัจจุบัน จากรายงานทางคลินิกแสดงความสัมพันธ์ระหว่างพหุสัณฐานของยีน CYP4A ในมนุษย์กับโรคเรื้อรัง ได้แก่ ภาวะจอตาเสื่อมในโรคเบาหวาน (diabetes retinopathy) ระดับไขมันในเลือดผิดปกติ และความดันเลือดสูง เป็นต้น ดังนั้นนิพนธ์ปริทรรศน์ฉบับนี้จึงมุ่งเน้นบทบาท การแสดงออก และผลกระทบทางคลีนิกที่มีนัยสำคัญของ CYP4A เพื่อเป็นข้อมูลพื้นฐานสำหรับการศึกษากลไกการควบคุมการแสดงออกของ CYP4A ในมนุษย์ และเป็นแนวทางในการทำนายภาวะแทรกซ้อนของโรคเรื้อรังจากพหุสัณฐานของ CYP4A

คำสำคัญ: ไซโตโครม พี 450 4 เอ, โอเมก้าไฮดรอกซิเลชัน, กรดอะราชิโดนิก, กรด 20-ไฮดรอกซีไอโคซาเตตระอีโนอิก, เพอรอกซิโซมโพรลิเฟอเรเตอร์แอกทิเวเตตรีเซปเตอร์แอลฟา, พหุสัณฐานของ CYP4A

CYP4A : Roles, Expression, and Clinical Impacts

Nathaphon Kuncharoenwirat[1,2], Kanokwan Jarukamjorn[2,3]*

[1] Undergraduate student (Doctor of Pharmacy, International Program), Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002 Thailand

[2] Research Group for Pharmaceutical Activities of Natural Products using Pharmaceutical Biotechnology (PANPB), Khon Kaen University, Khon Kaen 40002 Thailand

[3] Ph.D. (Pharmaceutical Sciences), Associate Professor, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002 Thailand

***Corresponding author:** Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002 Thailand.
Tel: 043-202305, Fax: 043-202379, Email: kanok_ja@kku.ac.th

Abstract

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Nathaphon Kuncharoenwirat[1,2], Kanokwan Jarukamjorn[2,3]*

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Cytochrome P450 4A enzyme (CYP4A) plays an important role in ω/ω-1 hydroxylation of fatty acids (FA). ω-Hydroxylation of arachidonic acid via CYP4A results in 20-hydroxyeicosatetraenoic acid (20-HETE), which is a potent vasoconstriction agent associated to cardiovascular disease. Hence, regulation of CYP4A expression is considered as a factor involved in the condition. Regarding the studies in rodents, regulatory expression of CYP4A is mediated by peroxisome proliferator activated receptor α (PPARα). After binding to a ligand, e.g. fibrates, plasticizers, and pesticides, the PPARα-ligand complex is formed and translocated to form a heterodimer with retinoid X receptor (RXR) in nucleus. The heterodimer bind with the specific base-sequences on peroxisome proliferator response element (PPRE) of CYP4A, followed by transcription of the gene. Nevertheless, this phenomenon does not occurred in human CYP4A, though human and rodents show very high percentage of base-sequences similarity. Regulatory mechanism of human CYP4A is presently unclear. Due to clinical reports, there is a relationship between polymorphism of human CYP4A and chronic diseases, e.g. diabetes retinopathy, abnormal lipid profile, and essential hypertension, etc. Therefore, this review focuses on significant role, expression, clinical impacts of CYP4A to be fundamental information for the study on regulation of human CYP4A expression and a guide to predict complications of chronic diseases associated CYP4A polymorphism.

Keywords: Cytochrome P450 4A, ω-hydroxylation, arachidonic acid, 20-hydroxyeicosatetraenoic acid, peroxisome proliferator activated receptor α, CYP4A polymorphism

1. Introduction to Cytochrome P450 Family 4 (CYP4)

Cytochrome P450 (CYP450) is a superfamily of hemoproteins mainly responsive for oxidative metabolism in phase I biotransformation with stereo- and region-specific enzymatic reaction pattern (Martignoni *et al.*, 2006; Sello *et al.*, 2015). CYP450 is not only the major enzyme superfamily that catalyzes oxidative biotransformation of many drugs and xenobiotics, but it also plays an important role on endogenous compounds which are steroid hormone biosynthesis, activation of vitamins A and D3, and metabolism of polyunsaturated fatty acid (FA), namely arachidonic acid (AA) and prostaglandins (Estabrook, 2003; Zanger and Schwab, 2013). In mammalian, CYP1, CYP2, CYP3, and CYP4 mostly metabolize xenobiotics and endogenous components, e. g. steroid, bile acid, FA, prostaglandins, eicosanoids, and retinoid whilst those of CYP5 and CYP8A play roles on biosynthesis of thromboxane and prostacyclin. CYP11, CYP17, CYP19, and CYP21 involve in steroid hormone synthesis whereas those classified as CYP7, CYP8B, CYP24, CYP27, CYP46, and CYP51 associate in biosynthesis pathways of bile acid, cholesterols, and vitamin D3. And CYP26 participates in retinoid metabolism (Honkakoski and Negishi, 2000).

CYP4, one of the oldest CYP450 families, has been discovered since 1987 to involve in metabolism of cholesterols. This family composes of 11 subfamilies from CYP4A to CYP4M that encode and express in both of mammals and insects but there are 6 subfamilies in human; 4A, 4B, 4F, and new discovered 4X, 4V, and 4Z (Simpson, 1997; Stark *et al.*, 2008). This review mentions CYP4A in human, rat, mouse, rabbit, and guinea pig, responsible for ω-hydroxylation of saturated and unsaturated FA, and biosynthesis of lipids (Simpson, 1997). Moreover, CYP4A metabolizes several kinds of prostaglandins. Role and significance of CYP4A, its regulatory mechanism, and clinical impact are included in this review.

2. Role and Significance of CYP4A

CYP4A is mostly found in kidney and liver and it shows low metabolic activity for xenobiotics (Kawashima *et al.*, 2000). Its plays an important role in metabolism of endogenous compounds, including medium chain FAs, saturated and unsaturated FAs, and some prostanoids, e.g. AA (Rettie and Kelly, 2008). Even CYP4A is responsible for endobiotics, drugs and xenobiotics also interact to the expression of CYP4A. Substrates of CYP4A are FAs which produce 19-hydroxyeicosatetraenoic acid (19-HETE) and 20-hydroxyeicosatetraenoic acid (20-HETE) by ω/ω-1 hydroxylation. Exposure to fibrates (hyperlipidemia drugs), β-napthoflavone, androgens, and diethyl phthalate (a plasticizer) induced CYP4A expression and increased the level of 20-HETE. On the other hand, 17-octadecynoic acid (17-ODYA), N-methylsulfonyl-12,12-dibromododec-11-enamide (DDMS), nitric oxide, superoxide, and carbon monoxide inhibited CYP4A enzyme (Imig, 2000; Fan *et al.*, 2015). 17-ODYA and DDMS reduced 20-HETE production via inhibition of ω-hydroxylation. As 17-ODYA mimics AA, it acts as suicide substrate inhibitor. Hence, 17-ODYA was not only selective to 20-HETE production, but it also inhibited formation of epoxyeicosatrienoic acids (EETs) from epoxidation via many CYP450s such as CYP1A1, CYP1A2, CYP2B1, CYP2C9, and CYP2E1. In contrast, DDMS was higher selective to ω-hydroxylation because DDMS contain methyl sulfimide with 12 carbons which was a preferable structure to CYP4A binding site (Wang *et al.*,1998; Imig, 2000; Frisbee *et al*, 2001; Nithipatikom *et al.*, 2004) as shown in Table 1.

CYP4A is normally located in endoplasmic reticulum and mostly functions with NADPH-dependent reaction (Capdevila *et al.*, 2005). ω/ω-1 hydroxylation is the character of CYP4A metabolism; it is an enzyme that performs high degree of regio-selective to substrates. When the substrate is metabolized, it becomes ω- and ω-1 alcohol. From a couple of studies, structures of saturated

FAs with C-12 to C-18 were the suitable lengths for CYP4A to undergo ω/ω-1 hydroxylation. The representative of C-12 FA is lauric acid. Even it rarely finds in mammalian tissue, it shows the faster rate of metabolism via CYP4A than AA (Capdevila *et al.*, 2005; Rettie and Kelly, 2008). The more increase in chain-length, the more decrease in catalytic rate and regio-selectivity was observed. All evidences were mostly occurred for human CYP4A11, and rabbit CYP4A5, CYP4A6, and CYP4A7 enzymes. (Rettie and Kelly, 2008)

Table 1. Drug interaction on CYP4A (Adapted from Fan *et al.*, 2015)

Substances	Categories	Result	References
Substrate			
Medium chain, saturated and unsaturated fatty acid (FA) - Arachidonic acid (AA)	Signaling molecule	ω,ω-1 Hydroxylation lead to 19-HETE, 20-HETE production	Fan *et al.*, 2015 Rettie and Kelly, 2008
Inducers			
Fibrates	Anti-hyperlipidemia	Increase 20-HETE	Fan *et al.*, 2015
Androgens	Male hormone		
Diethyl phthalate	Plasticizer		
β-napthoflavone	Ah-receptor agonist		
Inhibitors			
Nitric oxide	Cellular signaling	Decrease 20-HETE	Fan *et al.*, 2015
Carbon monoxide	Toxic gas		
Superoxide	Free radical		
17-octadecynoic acid (17-ODYA)	Fatty acid analog		Imig, 2000
N-methylsulfonyl-12,12-dibromododec-11-enamide (DDMS)	Selective CYP4A inhibitor		Imig, 2000

Note. Ah, Aryl hydrocarbon receptor; 20-HETE, 20-Hydroxyeicosatetraenoic acid

In general, CYP4A metabolized AA via ω-hydroxylation, resulted in production of 20-HETE (Roman, 2002; Gainer *et al.*, 2005; Lukaszewicz and Lombard, 2013; Fan *et al.*, 2015). There are 4 main roles of 20-HETE; 1) to be a potent vasoconstriction agent in renal and cerebral vessels, 2) to inhibit Ca^{2+}-dependent K^+ channel in vessels, 3) to control Na^+/K^+ ATPase activity, and 4) to control Ca^{2+} and Cl^- transportation (Capdevila *et al.*, 2005). As a potent vasoconstriction agent, 20-HETE is one of the key factors on vascular function associated to cardiovascular events (Lukaszewicz and Lombard, 2013) by promoting Ca^{2+} to enter the cell and blocking Ca^{2+}-sensitive K^+-channel (Figure 1). These events are resulting from activation of tyrosine kinase, Rho kinase, mitogen-activated protein kinases (MAPK), especially protein kinase C (PKC) (Fan *et al.*, 2015). After PKC is triggered, activation of G-rho is occurred, leading to an increase in regulation of L-type Ca^{2+}-channel. Moreover, a PKC actives G-Raf protein contributes to increase Ca^{2+}-sensitive K^+-channel activity and activates MAPK. Then activation of Ca^{2+}-sensitive K^+-channel leads to drop down of membrane potential which conducted the entering of Ca^{2+} via voltage-sensitive Ca^{2+} channel. Additionally, 20-HETE is not only activated PKC, but also raised phosphorylation of epithelial growth factor receptor (EGFR) via stimulating of Src intracellular proteins, leading to form the Shc, GRb, and Sos complex. From these step,

Sos activates GTPase protein p21ras, resulting in stimulating of Raf cascade and leading to cause inhibition of Ca^{2+}-sensitive K^{+}-channel as homeostasis. On the other hand, 20-HETE induces entering of non-selective cation via transient receptor potential canocical 6 channels contribute to artery auto-regulatory mechanism response (Imig, 2000; Roman, 2002; Fan *et al*., 2015). The vessel dysfunction and hypertensive event were also occurred by another pathway which is an increase in CYP4A expression. This leads to higher production of reactive oxygen species (ROS) such as peroxide (O^{-}_{2}) and endothelial nitric oxide synthase (eNOS) inactivation via rising of 20-HETE. Both of peroxide increment and eNOS inactivation result in lower nitric oxide (NO) level which is a cause of vasoconstriction (Wang *et al*., 2006).

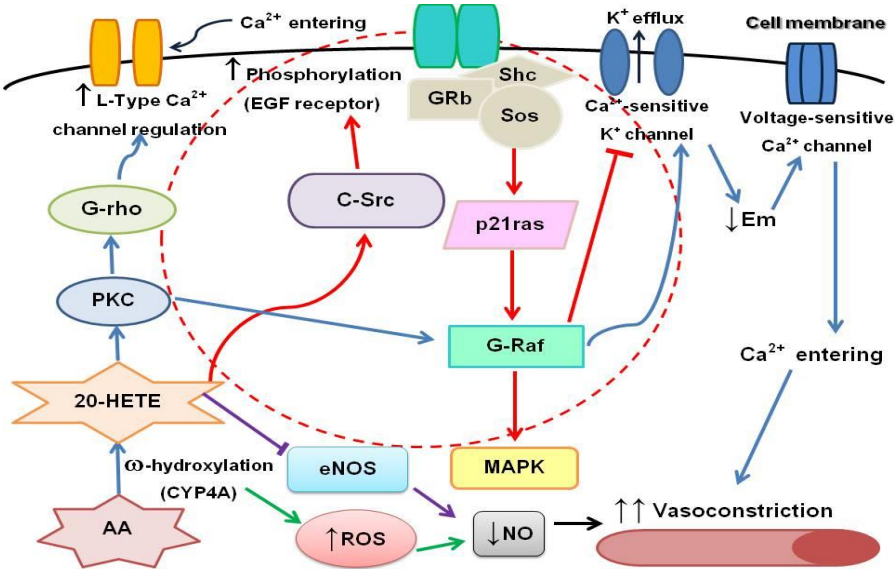

Figure 1 Vasoconstriction mechanism of 20-hydroxyeicosatetraenoic acid (20-HETE)
AA, arachidonic acid; PKC, protein kinase C; G-rho, G proteins rho; C-Src/Sch/GRb/Sos, Sr, Sgc, GRb, and Sos intracellular proteins; p21ras, GTPase protein p21ras; G-Raf, G-proteins Raf; MAPK, mitogen-activated protein kinase; Em, membrane potential; NO, nitric oxide; ROS, reactive oxygen spices; eNOS, endothelial nitric oxide synthase
(Adapted from Roman, 2002; Wang *et al*., 2006; Fan *et al*., 2015)

3. Regulation of CYP4A Expression

3.1. Expression of CYP4A

Human - Human CYP4A is located on the 1p33 region (the short arm of chromosome 1 at band 3 in region 3) (Vogel and Motulsky, 1997; Lino Cardenas *et al*., 2011). Human CYP4A enzymes include CYP4A11, CYP4A22, CYP4A26P, CYP4A27P, and CYP4A44P, in which CYP4A11 and CYP4A22 are true genes while CYP4A26P, CYP4A27P, and CYP4A44P are pseudogenes (Mittal *et al*., 2015). CYP4A11 and CYP4A22 cDNA regions show 94% sequence-similarity (Nelson *et al*., 2004; Rettie and Kelly, 2008) and they have similar intron along with exon size. However, some differences in nucleotide insertions and deletions of introns 1, 3, 9, and 11 at 610 bp, and 4, 6, and 11 at 618 bp, respectively, have been reported (Bellamine *et al*., 2003). CYP4A11 was more abundant than CYP4A22 (Rettie and Kelly, 2008) and the expression level of hepatic CYP4A11 was higher than in kidney about 2.5-fold (Graham *et al*., 2006; http://www.ncbi.nlm.nih.gov/genome). CYP4A was mostly exhibited at proximal tubule of kidney. By contrast, the expression of CYP4A11 was lower in a fetal liver by half of an adult kidney. CYP4A11 also expressed in other tissues, e. g. brain, lung,

reproductive organs (prostate, testis, uterus, and placenta), and small intestine, in a significantly 2 to 3 times lesser than in the liver (Graham *et al.*, 2006; Rettie and Kelly, 2008) (Table 2). Based on Genetic Analysis Package (GAP), rat *CYP4A1* noted the highest sequence-similarity (~87%) to human CYPA11 (Bell *et al.*, 1993) as show in Table 3.

Mouse - Mouse *Cyp4a* is the most variety of subfamily located on the 4D1 region (http://www.ncbi.nlm.nih.gov/genome). This subfamily consists of 8 isoforms, namely *Cyp4a10*, *Cyp4a12a*, *Cyp4a12b*, *Cyp4a14*, *Cyp4a29*, *Cyp4a30b*, *Cyp4a31*, and *Cyp4a32* with 2 pseudogenes, *Cyp4a28ps* and *Cyp4a30as* (Nelson *et al.*, 2004; Rettie and Kelly, 2008). Rat *CYP4A* showed very high identity to mouse *Cyp4a10* and *Cyp4a12* (81-93%) as show in Table 3. All *Cyp4a* of *129SvJ* female mouse plays a role on lauric acid hydroxylases (Capdevila *et al.*, 2005) whilst *Cyp4a12* functions on ω/ω-1 hydroxylase for AAs and acts as the main enzyme for 20-HETE production in the mouse kidney (Capdevila *et al.*, 2005; Rettie and Kelly, 2008). Expressions of *Cyp4a10, Cyp4a12*, and *Cyp4a14* are sexual dimorphism. Gonadectomy and sex hormone depletion down-regulated *Cyp4a10* and *Cyp4a14* in mouse liver and kidney but expression of *Cyp4a12a*[#1] in both liver and kidney and *Cyp4a12b*[#] in liver was increased (Zhang and Klaassen, 2013). *Cyp4a12a* was mostly expressed in the male whereas *Cyp4a14* was predominant in the female. Despite, *Cyp4a10* was found in kidney of both sexes; the expression was higher in the female than the male (Rettie and Kelly, 2008). Androgen up-regulated *Cyp4a12* expression in *Cyp4a14*-knockout male mice, leading to an increase in 20-HETE in the kidney and vessel, followed by an increase in systolic blood pressure (Savas *et al.*, 2003; Fan *et al.*, 2015).

Rat - Rat *CYP4A* includes *CYP4A1, CYP4A2, CYP4A3,* and *CYP4A8* (Marji *et al.*, 2002), located on the 5p35 region (http://www.ncbi.nlm.nih.gov/genome). *CYP4A1* and *CYP4A8* showed 76% sequence-identity (Table 3). *CYP4A2* and *CYP4A3* shared 98% sequence-identity but they play different roles on metabolism. *CYP4A2* highly metabolized AAs while *CYP4A3* showed no activity (Rettie and Kelly, 2008). Rat *CYP4A* mostly expressed in kidney and liver, and also found in brain, heart, lung, and placenta (Roman, 2002). In kidney, *CYP4A* highly expressed in proximal tubule as human CYP4A, but it can be found along nephrons at different levels. *CYP4A* exhibited ~1-4% in rat liver, but it was inducible up to 16-30% by fibrates (Simpson, 1997; Graham *et al.*, 2006). In lung, *CYP4A1* and *CYP4A2* expressed in smooth muscle cells and vessels such as bronchial smooth muscle and pulmonary arterial endothelial, respectively. Regarding placenta, *CYP4A1* is the highest expressed, follow by *CYP4A2, CYP4A3,* and *CYP4A4* (Rettie and Kelly, 2008). From the evolution of rodent species, rat *CYP4A1* and *CYP4A8* were homologs of mouse *Cyp4a10* and *Cyp4a12*. Moreover, rat *CYP4A2* and *CYP4A3* were defined as the homolog of mouse *Cyp4a14* (Capdevila *et al.*, 2005). Age is a factor related to rat *CYP4A* expression. The more aging, the lower expression of *CYP4A1* and *CYP4A3* were noted. In contrast, *CYP4A2* was undetectable before weaning period and it was increasingly expressed by age (Rettie and Kelly, 2008). Fibrates induced *CYP4A1* and *CYP4A3* in the kidney of male rat lower than in the liver while that of *CYP4A2* was at the same level in either kidney or liver (Simpson, 1997; Graham *et al.*, 2006). On the other hand, *CYP4A2* were undetectable in either liver or kidney of the female rat (Simpson, 1997). Androgen and testosterone up-regulated the expression of *CYP4A8* and *CYP4A2* (Simpson, 1997; Fan *et al.*, 2015) (Table 2).

Guinea pig - *CYP4A13* is a *CYP4A* in guinea pig. It shows 83% similarity to rat *CYP4A1* and 80% to rabbit *CYP4A4* (Bell *et al.*, 1993) (Table 3). The expression of *CYP4A13* was higher in male than female (Bell *et al.*, 1993).

Rabbit - There are four isoforms of *CYP4A* in rabbit, namely *CYP4A4, CYP4A5, CYP4A6,* and *CYP4A7* (Roman *et al.*, 1993). *CYP4A5* and *CYP4A7* were notably expressed in liver and kidney and both play a potential role on ω-hydroxylation and 20-HETE production. Furthermore, the expression of *CYP4A4* in the lung of pregnancy rabbit

[1#] *Cyp4a12* has 2 isoforms, namely *Cyp4a12a* and *Cyp4a12b*, found from tandem duplication (the mutation that produces the repeated two identical sequences in the same chromosome segment) at 100-kb in *Cyp4abx* cluster inside the mouse chromosome 4 (Nelson *et al.*, 2004).

exhibited over 100-fold to perform ω-hydroxylation specifically to prostaglandin E1 (PGE1) (Rettie and Kelly, 2008). Based on GAP calculation, *CYP4A4* shared 85% identity to human CYP4A11 (Bell *et al*., 1993) (Table 3).

Other mammalians - *CYP4A* can be found in other mammalians, e.g. dog and pig. Beagle dog expressed three isoforms of *CYP4A*, namely *CYP4A37*, *CYP4A38*, and *CYP4A39*, in kidney, liver, lung, intestine, skeletal muscle, and heart (Table 2). Beagle *CYP4A* exhibited 70% identity with rat *CYP4A1* and 78% with human CYP4A11 (Table 3). Pig expressed 4 isoforms of *CYP4A*, including *CYP4A21*, *CYP4A23*, *CYP4A24*, and *CYP4A25* (Bell *et al*., 1993; Lundell *et al*., 2001). Though pig *CYP4A21* showed 74% sequence-similarity to human CYP4A11 (Table 3), lauric acid hydroxylase activity was disappeared in pig. The evidence might cause from the different amino acid composition in the active binding site (Graham *et al*., 2006).

3.2. Regulatory mechanism of CYP4A expression

The expression of CYP4A, one of FA catabolism genes, involves with nuclear receptor mediated mechanism (Williams *et al*., 2005; Rettie and Kelly, 2008). Peroxisome proliferator activated receptors (PPARs) are nuclear hormone receptors activated by specific ligands, leading to gene transcription (Michalik *et al*., 2006). There are three isoforms of PPARs, namely PPARα, PPARγ, and PPARδ, but only PPARα plays a role as a mediator of CYP4A expression. PPARα mostly expresses in the liver and kidney where CYP4A is mostly found. Ligands of PPARα are divided into two groups which are peroxisome proliferator agents (PPs) and FAs (Wahli *et al*., 1995; Corton *et al*.; 2000; Williams *et al*., 2005). PPs, e.g. fibrates, plasticizers, trichloroacetic acid, and pesticides, are xenobiotics not involve in CYP4A metabolism, but they induce expression of CYP4A via PPARα-agonist activity (Williams *et al*., 2005). Likewise PPs, FAs include saturated and unsaturated FAs, e.g. AA, palmitic acid, and linoleic acid, are endogenous substances act as PPARα-agonist ligands (Corton *et al*.; 2000; Williams *et al*., 2005) and major substrates metabolized via CYP4A enzyme (Rettie and Kelly, 2008). They induce expression of CYP4A via PPARα-agonist activity (Williams *et al*., 2005). After a ligand binds with PPARα, the PPARα/ligand complex translocates to nucleus and performs dimerization with retinoid X receptor (RXR) to become heterodimer and occupy on the target gene which is cis-acting control element called peroxisome proliferator response elements (PPREs) (Simpson, 1997; Johnson *et al*., 2002; Williams *et al*., 2005; Graham *et al*., 2006). RXR can either bind 9-cis retinoic acid ligand or a free ligand, and leads to stimulate CYP4A gene expression via PPREs. Furthermore, not only ligand binding to PPREα but also the binding to RXR can induce the expression of CYP4A (Williams *et al*., 2005). In general, PPREs appear as two imperfect sequences which compose of repeated AGGTCA separated by one nucleotide which can be called DR1-motif together with (A/T)(A/T)CT sequences next on the 5'-upstream (Palmer *et al*., 1995; Johnson *et al*., 2002; Graham *et al*., 2006). Finally, when the PPARα/RXR complex activates PPRE, the expression of gene responsible for metabolism of FAs, especially CYP4A, is occurred (Figure 2). However, regulation of CYP4A expression via constitutive androstane receptor (CAR) and pregnane X receptor (PXR) are unclear and needed further study (Yoshinari *et al*., 2008).

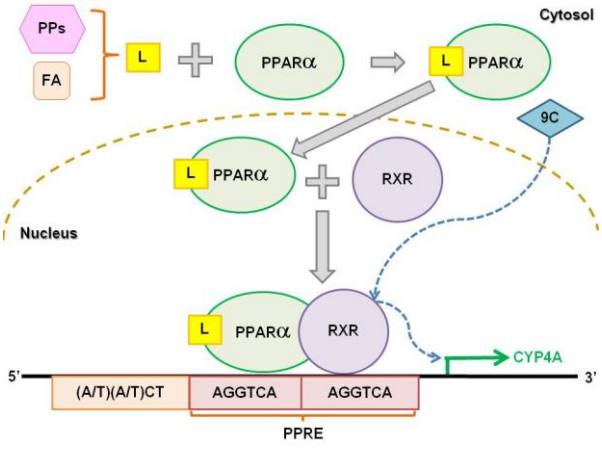

Figure 2 Regulatory mechanism of CYP4A expression via PPARα.
FA= fatty acids; PPs= peroxisome proliferator agents;
PPRE= peroxisome proliferator response element; L= ligands;
PPARα= peroxisome proliferator activated receptorα;
RXR= retinoid X receptor; 9C= 9-cis retinoic acid.
(Adapted from Nakamura *et al*., 2004; Williams *et al*., 2005; Graham *et al*., 2006)

Table 2. The comparison of CYP4A in each species, enzyme activity, and tissue distribution (Adapted from Simpson, 1997; Roman, 2002)

CYP4A	Tissue	Enzyme activity	Factor	References
Human (*Homo sapiens*)				
CYP4A11	L, K, B, LU, R, S	ω/ω-1 hydroxylation laurate and arachidonate	?	Bell *et al*., 1993; Simpson, 1997; Roman, 2002; Capdevila *et al*., 2005; Rettie and Kelly, 2008
CYP4A22	L,K	?	?	
Mouse (*Mus musculus*)				
Cyp4a10	L, K(F>M)	ω/hydroxylation of laurate	Fibrates(+), Testosterone(+), Growth hormone(+)	Bell *et al*., 1993; Simpson, 1997; Roman, 2002; Capdevila *et al*., 2005; Rettie and Kelly, 2008; Fan *et al*., 2015;
Cyp4a12	L, K (M>F), LU(M)	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+), Androgen(+)	
Cyp4a14	L, K(F>M)	ω-hydroxylation laurate	Fibrates(+), Androgen(+)	
Rat (*Rattus norvegicus*)				
CYP4A1	L, K, V, B, P, S	ω-hydroxylation laurate and arachidonate	Fibrates(+), Diabetes(+), Fasting (+), Age(-)	Bell *et al*., 1993; Simpson, 1997; Roman, 2002; Capdevila *et al*., 2005; Rettie and Kelly, 2008
CYP4A2	L, K, V, B, LU, P	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+), Diabetes(+), Fasting (+), Age(+), Testosterone(+)	
CYP4A3	L, K, V, B, LU, P	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+), Diabetes(+), Fasting (+), Age(-)	
CYP4A8	L, K, B, P, R	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+), Diabetes(+), Fasting (+), Androgen(+)	
Rabbit (*Oryctolagus cuniculus*)				
CYP4A4	L,K, P, R, LU(F>M)	ω/ω-1 hydroxylation laurate and arachidonate	Pregnancy(+), Steroid(+)	Bell *et al*., 1993; Simpson, 1997; Roman, 2002; Capdevila *et al*., 2005; Rettie and Kelly, 2008
CYP4A5	L, K, S	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+)	
CYP4A6	L, K	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+)	
CYP4A7	L, K, S	ω/ω-1 hydroxylation laurate and arachidonate	Fibrates(+)	
Guinea pig (*Cavia porcellus*)				
CYP4A13	L (M>F)	?	?	Bell *et al*., 1993; Simpson, 1997; Roman, 2002;
Dog *(Canis lupus)*				
CYP4A37	K, L, LU, S, H	ω-hydroxylation of fatty acid	Fibrates(+)	Graham *et al*., 2006
CYP4A38				
CYP4A39				

Note. B, Brain; H, Heart; K, Kidney; L, Liver; LU, Lung; P, Placenta; R, Reproductive organ; S, Small intestine; V, Vasculature; F, Female; M, Male; (+) Inducer; (-); Inhibitor ?, no known

Table 3. Percentage similarity of CYP4A isoforms by species (Adapted from Bell *et al*., 1993; Capdevila *et al*., 2005; Graham *et al*., 2006)

Species		% Identity								
		Rat				Rabbit	Dog			Pig
	CYP450	*CYP4A1*	*CYP4A2*	*CYP4A3*	*CYP4A8*	*CYP4A4*	*CYP4A37*	*CYP4A38*	*CYP4A39*	*CYP4A21*
Human	**CYP4A11**	87	80	80	83	85	78.2	78.8	78.6	74
Rat	***CYP4A1***	-	-	-	76	-	71.7	72.7	71.1	-
	CYP4A2	-	-	98	-	-	-	-	-	-
	CYP4A3	-	98	-	60	-	-	-	-	-
	CYP4A8	76	-	60	-	-	-	-	-	-
Mouse	***Cyp4a10***	93	84	84	81	86	-	-	-	-
	Cyp4a12	84	82	81	93	82	-	-	-	-
Guinea pig	***CYP4A13***	83	78	77	79	80	-	-	-	-

PPREs are defined in several species for encoding and regulating of CYP4A enzymes. For example, in rabbit there are two strong PPREs and one weak PPRE located around 677 bp on the upstream of *CYP4A6* gene. These PPRE regions interact with the PPARα/RXR complex and lead to *CYP4A6* transcription (Palmer *et al*., 1995; Johnson *et al*., 2002; Graham *et al*., 2006). Besides rabbit, rat has a PPRE located 4,300 bp on the upstream of *CYP4A1* gene responsible for *CYP4A1* expression after activation of the PPARα/RXR complex. There is another one element located on the upstream away from the aforementioned element, but this element does not interact with the PPARα/RXR complex. On the other hand, guinea pig and human are not found PPRE on the upstream of CYP4A (Graham *et al*., 2006). The differences between human and guinea pig with other rodents have been shown especially human; there is no known PPARα mechanism in human liver. Treatment of primary human hepatocytes with PPs such as hypolipidemic drugs demonstrated no induction of CYP4As, unlike that did in the rat. Correspondingly, PPs do not induced *CYP4A* in guinea pig. These observations indicated that this event may occurred from the different level of PPARα in human and guinea pig livers which exhibited 10 times lesser than that of the mouse liver (Johnson *et al*., 2002). The differences between species in both PPRE and PPARα affect expression of CYP4A, hence further study on relationship between PPARα and PPREs or other nuclear receptor-mediated transcription of CYP4A expression in human is of interest.

3.3. Polymorphism of CYP4A

Polymorphism of human CYP4A is a factor affecting catalytic activity related to cardiovascular disease. For example, two polymorphisms of human CYP4A11 845A>G and 8610T>C associated with coronary disease and arterial hypertension, respectively (Ogino *et al*., 2007; Lino Cardenas *et al*., 2011). Moreover, polymorphic 845A>G of CYP4A promoter region was a cause (~30%) of dwindling of transcription activity in Japanese CYP4A11, leading to a significant concomitant of hypertension event. The 845G allele showed different effect on ethnicity; a significant decrease in CYP4A11 transcription for 8% and 22.7% in French and Japanese, respectively, was noted (Sugimoto *et al*., 2008; Lino Cardenas *et al*., 2011). In addition, single nucleotide polymorphism at 8590T>C (a change of phenylalanine to serine at 434) associated with hypertension in Caucasians from Tennessee (US) and Augsburg (Germany), but not in Blacks (Gainer *et al*., 2005; Hiratsuka *et al*., 2006; Rettie and Kelly, 2008). There are 70 polymorphic variants of CYP4A11 in Korean: 60 in introns, 6 in exons, and 4 in 3'URT, 8590T>C (show as 8610T>C), but they showed unclear polymorphism related to hypertension (Cho *et al*., 2005; Rettie and Kelly, 2008). Regarding human CYP4A22, there are 20 variants from CYP4A22*2 to CYP4A22*15 in Japanese. Even CYP4A22*1 was a wide type, CYP4A22*5 allele is commonly appeared in Japanese. Furthermore, the protein at position 130 in human CYP4A22 has the great impact on the process of encoding functional protein; no encoding process of the functional protein was occurred if it has been exhibited glycine instead of serine. This event is the main point resulting CYP4A22 differed from the other CYP4As. In contrast, there are some CYP4A22 polymorphism containing serine at this position, e.g. CYP4A22*4, CYP4A 22*10, CYP4A22*12A, CYP4A22*12B, CYP4A22*13A, CYP4A22*13B, CYP4A22*14, and CYP4A22*15. Though CYP4A22 variants were found, all alleles expressed CYP4A22 enzymes had no catalytic activity on AA (Hiratsuka *et al*., 2006).

CYP4A11 plays a major role on AA metabolism, which is related to regulation of blood pressure. If CYP4A22 acts as CYP4A11 in the FA metabolism, CYP4A22 polymorphism would involve in blood pressure control. However, the role of human CYP4A22 is presently unclear (Hiratsuka *et al*., 2006; Lino Cardenas *et al*., 2011).

4. Clinical Impact of CYP4A

Diabetes type 2 is an important cause of organ damage, in which the main symptom is retinopathy which covers 2.5% of blindness worldwide (Bourne *et al*., 2013).

Type 2 diabetic Chinese patients with retinopathy (n= 395) and without retinopathy (n=415, as the control group) from Yantai Yeda Hospital from 2010 to 2014 were examined whether polymorphism of CYP4A11 T8590C allele related to type 2 diabetic retinopathy. The odd ratio (OR) between the CYP4A11 T8590C allele carriers and the controls was 1.6 (95%CI; 1.4-2.1, P=0.002). The results suggested that the patients who possessed CYP4A11 T8590C had higher risk (60%) of retinopathy (Sun *et al*., 2016). These findings revealed a hypothesis that the CYP4A11 T8590C polymorphism decreased 20- HETE synthase activity which affected retinal hemodynamic status. As 20- HETE is the vasoconstrictor, the decrease in 20-HETE formation resulted in lowering retinal blood flow and shear rate, consequently potentiated the risk of diabetic retinopathy due to retinal capillary occlusion (Wang *et al*., 2011; Sun *et al.,* 2016).

High density lipoprotein cholesterol (HDL-C) is known as a good lipid profile to transport lipid for metabolism in liver. The lower level of HDL-C, the higher risk of coronary heart disease was noted (Chapman *et al*., 2004). The Framingham offspring (807 men and 818 women) and BioVU (360 women and 348 men) at Vanderbilt University, Nashville, US, were studied correlation between CYP4A11 T8590C and HDL-level. There was no correlation between CYP4A11 T8590C allele on the HDL-C level in overall patients. Interestingly, CYP4A11 8590C allele significantly increased the event of lower HDL-C level in the women with OR of 1.39 (95% CI; 1.02-1.90, *P*=0.02) from the Framingham offspring and OR of 1.69 (95% CI; 1.03-2.77, *P*=0.04) from the BioVU. These evidences supported that CYP4A11 8590C allele polymorphism increased the risk of coronary heart disease in women around 39-69% by lowering HDL-C level (White *et al*., 2013). The possible hypothesis is CYP4A11 T8590C polymorphism results in lowering CYP4A11 ω-hydroxylation activity. Hydroxy-epoxyeicosatrienoic acid (HEET), a product from CYP4A ω-hydroxylation of EET, is an endogenous potent PPARα agonist. The more deficiency of HEETs, the less of apolipoprotein A-I and A-II encoding via PPARα was occurred, leading to a decrease in HDL formation (White *et al*., 2013; Sun *et al*., 2016).

Essential hypertension is an important risk factor for cardiovascular disease such as stroke and myocardial infarction, subsequently resulting in an increased risk of mortality and morbidity events (Suzuki and Kanno, 2005). Relationship between CYP4A11 polymorphism and essential hypertension was examined in Zhengzhou University hospital (1648 participants from 42 to 70 years old during January 2011 to November 2013). The participants composed of 2 groups, 820 with essential hypertension and 828 with normal blood pressure. The patients carried C allele (TC and CC) polymorphism on CYP4A11 rs1126742 showed a significant increase in the risk of essential hypertension of the diastolic blood pressure compared with those carried TT allele as OR of 1.56 (95%CI; 1.24–1.91). In addition, the patients with G allele (CG and GG) polymorphism on CYP4A11 rs3890011 showed a significant increase in essential hypertension of the systolic blood pressure compared with those carried CC allele with OR of 1.31 (95%CI; 1.15–2.03). These observations suggested that the patients with C allele on CYP4A11 rs1126742 and G allele on CYP4A11 rs3890011 possessed the higher risk of essential hypertension for 56% and 31%, respectively (Zhang *et al*., 2017). The hypothesis of this event is polymorphism of CYP4A11 T8590C leads to a decrease in 20-HETE synthase activity in the kidney. At the proximal tubules and the thick ascending loop of Henle, 20-HETE plays a critical role in inhibition of Na^+ transportation channel, therefore a decrease in 20-HETE results in an increase of Na^+ retention, consequently develops salt sensitive hypertension (Sun *et al*., 2016; Zhang *et al*., 2017).

Cancer metastasis is a major cause of death. Tumor-associated macrophages (TAMs) are inflammatory stromal cells usually found in tumor cells and play important roles on cancer cell metastasis (Chen and Bonaldo, 2013). The immunohistochemistry (IHC) score of 5 benign breast diseases, 6 noninvasive breast carcinoma, and 87 invasive breast carcinoma showed that expression of CYP4A protein

were significantly greater in invasive breast carcinoma than others two groups (P<0.01). Regarding, the IHC score in 4 normal skin, 4 benign and 27 melanoma tissue, CYP4A was expressed at the significantly higher level in melanoma tissues than the normal tissues (P<0.05). Moreover, the survey of clinical outcomes from 780 patients with invasive breast cancer and 71 patients with melanoma showed that the breast cancer patients with high level of CYP4A22 exhibited lower number of recurrence-free survival patients than those with low expression of CYP4A22 (Log-rank P=0.0485). Similarly, high expression of CYP4A11 in melanoma patient significantly lowered number of recurrence-free survival patients than one with low CYP4A11 expression (Log-rank P=0.0313) (Chen *et al*., 2017). These observations supported that the higher expression of CYP4A might be one of the factors associated with metastasis of cancer cells in human.

5. Conclusion

CYP4A plays a major role on ω/ω-1 hydroxylation of medium chain FAs. Hence, CYP4A is not only responsible for metabolism of FA, but also biosynthesis of signaling molecules in the body. For example, 20-HETE, a well-known product from ω-hydroxylation of AA by CYP4A, is a potent vasoconstriction agent associated to the main risk of cardiovascular disease. Therefore, regulation of CYP4A expression becomes one of interested topics nowadays. Regulatory pathway of CYP4A has been extensively studied in rodents. It is generally regulated by nuclear receptor-mediated mechanism beginning with a ligand of PPARα, e.g. FAs, fibrates, plasticizers, trichloroacetic acid, and pesticides, formed the PPARα-ligand complex, before dimerization with RXR, followed by occupying at the PPRE region of the gene and leading to CYP4A transcription. Interestingly, this exposure to aforementioned ligands did not observe the induction on human CYP4A expression, though the high percentage of sequence-similarity and the same expression organs (liver and kidney) were noted among rodents, other mammalians, and human. There are some possible hypotheses to explain the induction of CYP4A in differences species. Firstly, human PPARα in the liver is 10 times lower than other rodents except guinea pig. Secondly, disappearance of PPRE region on the 5'-upstream of human CYP4A gene was noted. Thirdly, differences of amino acid composition at the active binding site from genetic variation change catalytic activity of the enzyme.

Currently, regulatory mechanism of human CYP4A is unclear. Human CYP4A related-clinical outcomes, especially CYP4A11 polymorphism, were reported from the fields. Human CYP4A11 polymorphisms associated with chronic diseases such as diabetic retinopathy, abnormal lipid profile, and hypertension. Hypertension associated with CYP4A11 polymorphism has been found in both Asian and Caucasian. For example 845A>G CYP4A11 polymorphic was related to concomitant hypertension in 30% of Japanese while 8590T>C CYP4A11 polymorphism in U.S. and China led to hypertension, lower HDL-level, and diabetic retinopathy. Though regulatory mechanism of human CYP4A expression was unclear and different from other animals, clinical evidences regarding CYP4A polymorphism and its function on blood pressure control related to hypertension has assured the importance of human CYP4A. Eventually, knowledge of *CYP4A* regulation in rodents and other animals can help as a guide for prediction and/or explanation. Hence, a humanized animal model or a gene modified human cell line is of interest to develop as a model to unravel regulatory mechanism of human CYP4A expression.

References

Bell DR, Plant NJ, Rider CG, *et al*. Species- specific induction of cytochrome P- 450 4A RNAs: PCR cloning of partial guinea pig, human, and mouse CYP4A cDNAs. *Biochem J* 1993; 294(Pt 1): 173-180.

Bellamine A, Wang Y, Waterman MR, *et al*. Characterization of the CYP4A11 gene, a second CYP4A gene in humans. *Arch Biochem Biophys* 2003; 409(1): 221-227.

Bourne RR, Stevens GA, White RA, *et al*. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *Lancet Glob Health* 2013; 1(6): e339-349.

Capdevila JH, Holla VR, Faick JR. Cytochrome P450 and the metabolism and bioactivation of arachidonic acid and eicosanoids. In: Ortiz de Montellano PR, editor. Cytochrome P450. 3rd ed. New York: Kluwer Academic/Plenum Publishers; 2005. 531-532.

Chapman MJ, Assmann G, Fruchart JC, Shepherd J, Sirtori C, European Consensus Panel on HDL-C. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid --a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; 20(8): 1253-1268.

Chen P, Bonaldo P. Role of macrophage polarization in tumor angiogenesis and vessel normalization: implications for new anticancer therapies. *Int Rev Cell Mol Biol* 2013; 301: 1-35.

Chen XW, Yu TJ, Zhang J, *et al*. CYP4A in tumor-associated macrophages promotes pre-metastatic niche formation and metastasis. *Oncogene* 2017*;* 36(35): 5045-5057.

Cho BH, Park BL, Kim LH, Chung HS, Shin HD. Highly polymorphic human CYP4A11 gene. *J Hum Genet* 2005; 50(5): 259–263.

Corton JC, Anderson SP, Stauber A. Central role of peroxisome proliferator-activated receptors in the actions of peroxisome proliferators. *Annu Rev Pharmacol Toxicol* 2000; 40: 491-518.

Estabrook RW. A passion for P450s (remembrances of the early history of research on cytochrome P450). *Drug Metab Dispos* 2003; 31(12): 1461–1473.

Fan F, Muroya Y, Roman RJ. Cytochrome P450 eicosanoids in hypertension and renal disease. *Curr Opin Nephrol Hypertens* 2015*;* 24(1): 37-46.

Frisbee JC, Roman RJ, Falck JR, Krishna UM, Lombard JH. 20-HETE contributes to myogenic activation of skeletal muscle resistance arteries in Brown Norway and Sprague–Dawley rats. *Microcirculation* 2001; 8(1): 45-55.

Gainer JV, Bellamine A, Dawson EP, *et al*. Functional variant of CYP4A11 20-Hydroxyeicosatetraenoic acid synthase is associated with essential hypertension. *Circulation* 2005; 111(1): 63-69.

Graham RA, Goodwin B, Merrihew RV, Krol WL, LeCluyse EL. Cloning, tissue Expression, and regulation of beagle dog CYP4A genes. *Toxicol Sci* 2006; 92(2): 356-367.

Hiratsuka M, Nozawa H, Katsumoto Y, *et al*. Genetic polymorphisms and haplotype structures of the CYP4A22 gene in a Japanese population. *Mutat Res* 2006; 599(1-2): 98–104.

Honkakoski P, Negishi M. Regulation of cytochrome P450 (CYP) genes by nuclear receptors. *Biochem J* 2000; 347(Pt 2): 321-337.

Imig JD. Eicosanoid regulation of renal vasculature. *Am J Physiol Renal Physiol* 2000; 279(6): F965-F981.

Johnson EF, Hsu M, Savas U, Griffin KJ. Regulation of P450 4A expression by peroxisome proliferator activated receptors. *Toxicology* 2002; 181–182: 203–206.

Kawashima H, Naganuma T, Kusunose E, *et al*. Human fatty acid ω-hydroxylase, CYP4A11: Determination of complete genomic sequence and characterization of purified recombinant protein. *Arch Biochem Biophys* 2000; 378(2): 333-339.

Lino Cardenas CL, Renault N, Farce A, *et al*. Genetic polymorphism of CYP4A11 and CYP4A22 genes and in silico insights from comparative 3D modelling in a French population. *Gene* 2011*;* 487(1): 10–20.

Lundell K, Hansson R, Wikvall K. Cloning and expression of a pig liver taurochenodeoxycholic acid 6alpha-hydroxylase (CYP4A21): a novel member of the CYP4A subfamily. *J Biol Chem* 2001; 276(13): 9606-9612.

Lukaszewicz KM, Lombard JH. Role of the CYP4A/20-HETE pathway in vascular dysfunction of the Dahl salt-sensitive rat. *Clin Sci (London)* 2013; 124(12): 695-700.

Marji JS, Wamg M, Laniado-Schwartzman M. Cytochrome P-450 4A isoform expression and 20-HETE synthesis in renal preglomerular arteries. *Am J Physiol Renal Physiol* 2002; 283(1): F60–F67.

Martignoni M, Groothuis GM, de Kanter R. Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. *Expert Opin Drug Metab Toxicol* 2006; 2(6): 875-894.

Michalik L, Auwerx J, Berger JP, *et al*. International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacol Rev* 2006; 58(4): 726–741.

Mittal B, Tulsyan S, Kumar S, Mittal RD, Agarwal G. Cytochrome P450 in cancer susceptibility and treatment. In: Makowski GS, editor. Advances in clinical chemistry volume 71. Oxford: Elsevier Inc.; 2015. 79-83.

Nakamura MT, Cheon Y, Li Y, Nara TY. Mechanisms of regulation of gene expression by fatty acids. *Lipids* 2004; 39(11): 1077-1083.

Nelson DR, Zeldin DC, Hoffman SMG, Maltais LJ, Wain HM, Nebert DW. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics* 2004; 14(1): 1-18.

Nithipatikom K, Gross ER, Endsley MP, *et al*. Inhibition of Cytochrome P450-hydroxylase a novel endogenous cardioprotective pathway. *Circ Res* 2004; 95(8): e65-e71.

Ogino S, Gulley ML, den Dunnen JT, Wilson RB, Association for Molecular Patholpogy Training and Education Committtee. Standard mutation nomenclature in molecular diagnostics. *J Mol Diagn* 2007; 9(1): 1–6.

Palmer CNA, Hsu MH, Griffin KJ, Johnson EF. Novel sequence determinants in peroxisome proliferator signaling. *J Biol Chem* 1995; 270(27): 16114–16121.

Rettie AE, Kelly EJ. The CYP4 Family. In: Ioannides C, editor. Cytochromes P450: Role in the metabolism and toxicity of drug and other xenobiotics. Cambridge: The Royal Society of Chemistry; 2008. 385-394.

Roman RJ. P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev* 2002; 82(1): 131–185.

Roman LJ, Palmer CN, Clark JE, *et al*. Expression of rabbit cytochromes P4504A which catalyze the omega-hydroxylation of arachidonic acid, fatty acids, and prostaglandins. *Arch Biochem Biophys* 1993; 307(1): 57-65.

Savas U, Hsu M, Johnson EF. Differential regulation of human CYP4A genes by peroxisome proliferators and dexamethasone. *Arch Biochem Biophys* 2003; 409(1): 212-220.

Sello MM, Jafta N, Nelson DR, *et al*. Diversity and evolution of cytochrome P450 monooxygenases in Oomycetes. *Sci Rep* 2015; 5: 11572.

Simpson AE. The Cytochrome P450 4 (CYP4) family. *Gen Pharmacol* 1997; 28(3): 351-359.

Stark K, Dostalek M, Guengerich FP. Expression and purification of orphan cytochrome P450 4X1 and oxidation of anandamide. *FEBS J* 2008; 275(14): 3706–3717.

Sugimoto K, Akasaka H, Katsuya T, *et al*. A polymorphism regulates CYP4A11 transcriptional activity and is associated with hypertension in a Japanese Population. *Hypertension* 2008; 52(6): 1142-1148.

Suzuki H, Kanno Y. Efficacy of can desartan on outcome in Saitama trial (E-COST) group: Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005; 28(4):307–314.

Sun XF, Wang XJ, Yang YY. Association of CYP4A11 gene polymorphism with diabetic retinopathy in Chinese patients. *Int J Clin Exp Med* 2016; 9(9): 18346-18352.

Vogel F, Motulsky AG. Vogel and Motulsky's Human Genetics: Problems and approaches. 3rd ed. Heidelberg: Springer-Verlag Berlin Heidelberg; 1997. 58-60.

Wahli W, Braissant O, Desvergne B. Peroxisome proliferator activated receptors: Transcriptional regulators of adipogenesis, lipid metabolism and more. *Chem Biol* 1995; 2(5): 261-266.

Wang J, Singh H, Zhang F, *et al*. Endothelial dysfunction and hypertension in rats transduced with CYP4A2 adenovirus. *Circ Res* 2006; 98(7): 962-969.

Wang M, Brand-Schieber E, Zand BA, *et al*. Cytochrome P450-derived arachidonic acid metabolism in the rat kidney: Characterization of selective inhibitors. *J Pharmacol Exp Ther* 1998; 284(3): 966-973.

Wang Z, Yadav AS, Leskova W, Harris NR. Inhibition of 20-HETE attenuates diabetes-induced decreases in retinal hemodynamics. *Exp Eye Res* 2011; 93(1): 108-113.

White CC, Feng QP, Cupples LA, *et al*. CYP4A11 variant is associated with high density lipoprotein cholesterol in women. *Pharmacogenomics J* 2013; 13(1): 44–51.

Williams SN, Dunham E, Bradfield CA. Induction of Cytochrome P450 enzymes. In: Ortiz de Montellano PR, editor. Cytochrome P450 Structure, Mechanism, and Biochemistry. New York: Kluwer Academic/Plenum Publishers; 2005. 323-339.

Yoshinari K, Tien E, Negishi M, Honkakoski P. Receptor-mediated regulation of Cytochromes P450. In: Ioannides C, editor. Cytochromes P450: Role in the Metabolism and Toxicity of Drug and other Xenobiotics. Cambridge: The Royal Society of Chemistry; 2008. 418-439.

Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013; 138(1): 103-141.

Zhang H, Jin L, Mu T, *et al*. Associations of CYP4A11 gene–gene and gene–smoking interactions with essential hypertension in the male eastern Chinese Han population. *Clin Exp Hypertens* 2017; 39(5): 448–453.

Zhang Y, Klaassen CD. Hormonal regulation of Cyp4a isoforms in mouse liver and kidney. *Xenobiotica* 2013; 43(12): 1055–1063.