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Research Article

The Synergistic and Opposing Roles of ω-Fatty Acid Hydroxylase (*CYP4A11*) and ω-1 Fatty Acid Hydroxylase (*CYP2E1*) in Chronic Liver Disease

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Abstract

Cytochrome P450 fatty acid hydroxylase consists of members of the CYP4 family that ω-hydroxylate fatty acids and the *CYP2E1* that ω-1 hydroxylates fatty acids. Although ω and ω-1 hydroxylation of fatty acids have been thought to play a minor role in fatty acid metabolism (less than 20%), it plays a vital role in excess liver fatty acids overload seen in fasting, diabetes, metabolic disorder, and over-consumption of alcohol and high-fat diet. This pathway provides anabolic metabolites for gluconeogenesis, succinate, and acetate for lipogenesis. The *CYP4A* and *CYP2E1* genes are activated in fasting and several metabolic disorders, suggesting a synergistic role in preventing fatty acid-induced lipotoxicity with the consequence of increased liver cholesterol and lipogenesis leading to increased Lipid Droplet (LD) deposition. During the progression of Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD), activation of Phospholipase A2 (PLA_2) releases arachidonic acid that *CYP4A11* and *CYP2E1* P450s metabolize to produce 20-hydroxyeicosatetraenoic acid (20-HETE) and 19-HETE, respectively. These metabolites have opposing roles in the progression of MASLD and chronic liver disease (CLD). This report discusses the synergistic role of the CYP4A and *CYP2E1* P450s in the metabolism of saturated and unsaturated fatty acids and their opposite physiological role in the metabolism of Arachidonic Acid (AA). We finally discuss the role of ethanol in disrupting the synergistic and opposing roles of the *CYP4A* and *CYP2E1* genes in MASLD and CLD.

Abbreviations

AA: Arachidonic Acid; ACAA1: Acetyl-CoA Acyltransferase 1; ACOX1: Acyl-CoA Oxidase; ACOT4: Acyl-CoA Thioesterase 4; ACOT8: Acyl-CoA Thioesterase 8; ACOT12: Acyl-CoA Thioesterase 12; ACE: Angiotensin-Converting Enzyme; ACLD: Acute on Chronic Liver Disease; ADH4: Alcohol Dehydrogenase 4; ALDH3A2: Aldehyde Dehydrogenase 3A2; ACSVL4: Acyl-CoA Synthetase Very Long Chain 4; ABCD3: ATP Binding Cassette Subfamily D Member 3; CD36: Cluster of Differentiation 36; CLD: Chronic Liver Disease; COX1/2: Cyclooxygenase 1/2; *CYP4A11*: Cytochrome P450 Family 4; *CYP2E1*: Cytochrome P450 2 Family; DCA: Dicarboxylic Acid; 11,12 DiHETrE: 11,12-Dihydroxy-5Z,8Z,14Z-Eicosatrienoic Acid; ECM: Extracellular Matrix; EET: 2-Enoyl-CoA Hydratase, 3-Hydroxyacyl-CoA Dehydrogenase, EEHADH; EET: Epoxyeicosatrienoic Acid; EGFR: Epidermal Growth Factor Receptor; eNOS: Endothelial Nitric Oxide Synthase; FATP4: Fatty Acid Transport Protein 4; ERS: Endoplasmic Reticulum Stress; Km: Affinity Substrate for Enzyme; GPR75: G-Coupled Protein Receptor 75; FAO: Fatty Acid Oxidation; FFAR1: Free Fatty Acid Receptor 1; FFA: Free Fatty Acid; GSE: Gene-Expression Data Sets; HCC: Hepatocellular Carcinoma; HSC: Hepatic Stellate Cells; 20-HETE: 20-Hydroxyeicosatetraenoic Acid; 12-HHT: 12-(S)-Hydroxy-5Z,8E,10E-Heptadecatriaenoic Acid; HSD17B4: 17β-Hydroxysteroid Dehydrogenase 17B4; HODE: 13(S)-Hydroxy-9Z,11E-Octadecadienoic Acid; IL1: Interleukin 1; IL6: Interleukin 6; IPR: Prostacyclin Receptor;

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LRE: Linear Regression of Efficiency; LSEC: Liver Sinusoidal Endothelial Cells; MAPK: Mitogen-Activated Protein Kinase; MASH: Metabolic Dysfunction Steatosis Hepatitis; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; MCD: Methionine Choline-Deficient Diet; MRP2: Multi-Drug Resistance Associated Transport Protein 2; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; NEFA: Non-Esterified Fatty Acids; NF-κβ: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; NrF2: Nuclear Erythroid Factor 2; NSBB: Non-Selective Beta Blockers; PKA: Protein Kinase A; PGG2: Prostaglandin Endoperoxidase; PGH2: Prostaglandin Hydroquinone 2; PGE2: Prostaglandin E2; PVT: Portal Vein Thrombosis; RAS: Renin-Angiotensin System; SCPx: Sterol Carrier Protein X; TGF-β1: Transforming Growth Factor Beta 1; VEGF: Vascular Endothelial Growth Factor

Introduction

The Human cytochrome P450 family consists of 57 individual P450s that metabolize drugs and environmental toxins. However, these cytochrome P450s also have a pivotal role in metabolizing endogenous molecules, including vitamins, cholesterol, bile acids, steroids, fatty acids, and bioactive eicosanoids [1]. The eicosanoid arachidonic acid is converted to pro-inflammatory leukotrienes that Human CYP4F family members inactivate, while pro-inflammatory 20-HETE is synthesized from arachidonic acid by *CYP4A11*. The 20-HETE eicosanoid is a high-affinity ligand for the GPR75 receptor that activates the NFκβ pathway, leading to inflammation [2]. GPR75 activation by 20-HETE causes vasoconstriction by activating Angiotensin II [3], Furthermore, 20-HETE has been implicated in activating liver stellate cells and fibrosis [4]. A recent report from a large-scale human exome study revealed that GPR75 loss-of-function variants are associated with lower body fat and BMI [5]. In mice, inactivation of GPR74 prevents dietary-induced obesity, and loss of function protects against fatty liver disease [6].

CYP4A11 is a highly polymorphic gene with overexpression in humans that increases 20-HETE serum levels associated with hypertension and plaque in patients with ischemic stroke [7]. The expression of *CYP4A11* and 20-HETE levels has not been analyzed in patients with Metabolic Dysfunction-associated Steatosis Liver Disease (MASLD). Unfortunately, there have been no studies on the 20-HETE-producing *CYP4a12* in mice. *CYP4a14* $^{-/-}$ mice resist hypertension and high fat diet-induced fatty liver disease even though *CYP4a14* P450 does not metabolize arachidonic acid to 20-HETE [8]. It is suggested that stressors such as fasting or a high-fat diet activation of *CYP4a14* increase the level of *CYP4a12* and 20-HETE, leading to increased hypertension and diet-induced fatty liver disease [9].

In contrast to the ω-hydroxylation of arachidonic acid to 20-HETE, the ethanol-inducible *CYP2E1* metabolizes arachidonic acid to ω-1 arachidonic metabolite 19-HETE [10]. *CYP2E1* P450 has been implicated in alcoholic-associated liver disease through its generation of Reactive Oxygen Species (ROS), leading to lipid peroxidation. However, the role of 19-HETE produced by *CYP2E1* P450 has not been explored in association with alcoholic-associated or metabolic-associated fatty liver disease. 19-HETE is a potent prostacyclin receptor agonist that inhibits platelet aggregation, angiotensin II-induced hypertension, and fibrosis when activated while inducing vasodilation [11,12]. In this review, we explore the opposite and contrasting roles of *CYP4A11* ω-hydroxylated 20-HETE, and the *CYP2E1* ω-1 hydroxylated 19-HETE in the context of chronic liver disease.

Although *CYP4A11* 20-HETE and *CYP2E1* 19-HETE have opposing physiological roles, both cytochrome P450s have a synergistic and similar role in the metabolism of fatty acids. Hydroxylated fatty acids are sequentially metabolized by alcohol and aldehyde dehydrogenases to Dicarboxylic Acid (DCA), transported into the peroxisome, and chain-shortened by β-oxidation. Successive rounds of peroxisome β-oxidation produce shorter chain DCA, which is either transported to mitochondria for complete β-oxidation or functions as anaplerotic metabolites for gluconeogenesis or lipogenesis, resulting in Lipid Droplet (LD) formation and hepatic steatosis.

In this review, we discuss the opposing and contrasting roles of *CYP4A11* and *CYP2E1* in the metabolism of arachidonic to 20-HETE and 19-HETE, which have opposing physiological roles through activation of GPR75 and prostacyclin (IP) receptors, respectively. We also explore the similar and synergistic role of the *CYP4A11* and *CYP2E1* P450s in the metabolism by analyzing the catalytic activity of these P450s in the metabolism of arachidonic and saturated fatty acids. We identify the possible role of CYP P450 arachidonic acid and fatty acid metabolites in diabetic hyperglycemia, LD formation in hepatic steatosis, and their functional role in hypertension through their effect on hepatic hepatocytes, stellate, and endothelial cells. Finally, we discuss the function of *CYP4A11* and *CYP2E1* saturated fatty acid metabolites serving as anaplertoic metabolites for fatty acid and cholesterol synthesis leading to increased lipid droplet formation in hepatic steatosis. We also detail the role of the *CYP4A11* and *CYP2E1* arachidonic metabolites and their possible functional role in portal hypertension in hepatic cirrhosis and suggest alteration in these pathways may be therapeutic targets in the treatment of chronic liver disease.

Background

Omega and Omega-1 cytochrome P450 hydroxylase in fatty acid metabolism

Fatty acid omega (ω) and omega-1 (ω-1) cytochrome P450 hydroxylases are considered to have a minor role in the metabolism of fatty acids; however, their importance increases in fasting and several disease states, including diabetes [13-16], contributing up to 20% of fatty acid oxidation (Figure 1). *CYP4A11* P450 binds saturated lauric acid (C12:0) with a Km of 4.7 μM, and Kcat of 7 min^{-1}, while *CYP2E1* binds with a Km 84μM and Kcat of 3.8 min^{-1} [10,17], far below the plasma levels of palmitic and stearic acid (0.03-4 mM) observed in human plasma. Alcohol dehydrogenase ADH4 binds fatty acids with a Km of 10-20 μM and cytosolic aldehyde dehydrogenase ALDH3A2, also known as Fatty Aldehyde Dehydrogenase

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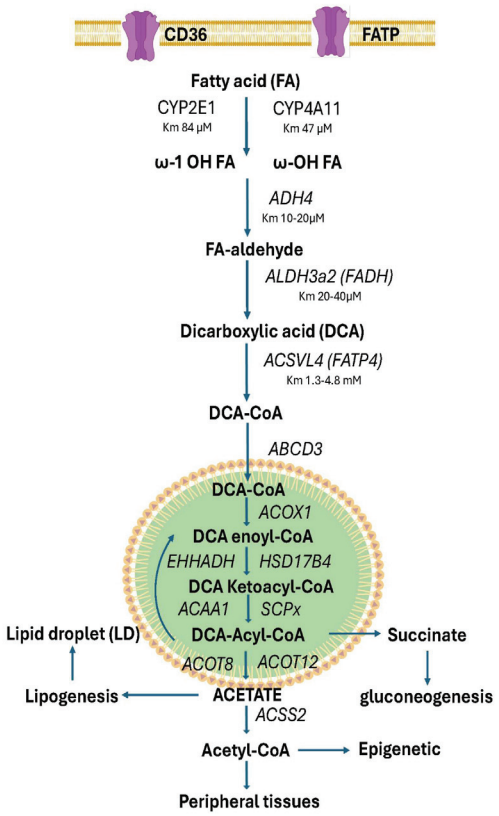

Figure 1: The synergistic role of Omega P4504A11 and Omega-1 P4502E1 hydroxylation of saturated fatty acids and further metabolism by peroxisome β-oxidation. CYP4A11 P450 has a lower Km for saturated fatty acids than CYP2E1 P450. Microsomal alcohol dehydrogenase (ADH4) and Aldehyde Dehydrogenase (ALDH3a2) have similar Km values for hydroxylated fatty acids. Also, the oxidation rates of their enzymatic activities are linked to the metabolism of hydroxylated fatty acids. Dicarboxylic Acid (DCA) accumulates in the cytosol because Acyl-CoA synthetase (ACSVL4) has a high Km. ABCD3 transports DCA into mitochondria to be metabolized by Acyl-CoA oxidase 1 (ACOX1) and the peroxisomal bifunctional hydratase/dehydrogenase (EHHAH-HSD17B4). Acetyl-CoA is released from Acyl-CoA by acetyl-CoA acyltransferase (ACCA1) or SCPx thiolase. Acetate is formed from acetyl-CoA by acyl-CoA thioesterase 12 (ACOT12) or acyl-CoA thioesterase 8 (ACOT8). The acyl-CoA, succinate is released from succinyl-CoA by ACOT4. Acetate can be used as an energy source by peripheral tissues or in hepatocytes as a substrate for fatty acid or cholesterol synthesis, resulting in Lipid Droplet (LD) formation. Mitochondria can use succinate in fasting for gluconeogenesis. Both succinyl-CoA and acetyl-CoA are substrates that may epigenetically modify chromatin structure through epigenetic compartmentalization of epigenetic metabolites.

(FALDH) binds fatty acids with Km of 20-40 µM [18]. It is of interest that, unlike other aldehyde dehydrogenases, ALDH3A2 and 3B2 use $NADP^+$ as a cofactor and, therefore, can regenerate NADPH for cytochrome P450 metabolism of the fatty acid substrates. In addition, the tight association of ADH and ALDH3A2 in microsomes makes for an efficient system to eliminate reactive aldehydes. The microsomal long-chain Fatty Acid Transport Protein 4 (FATP4, ACSVL4) converts the Dicarboxylic Acids (DCAs) to their respective CoAs and binds C16:0 to C24:0 with Km of 13 to 4.8 mM [19].

The DCA-CoA is transported into the peroxisome by the 70-KDa peroxisomal membrane protein (PMP70, ABCD3) [20,21]. Acyl-CoA oxidase (ACOX1) catalyzes the first step in peroxisome β-oxidation while the L- and D-bifunctional protein enoyl-CoA hydratase (EEHADH) and 3-hydroxyacyl CoA dehydrogenase 17B4 (HAD17B4), respectively, catalyze the hydratase/dehydrogenase steps in the β-oxidation of fatty acids with EEHADH having a 3-fold lower affinity for DCA-CoA [22]. The thiolase, sterol carrier protein x (SCPx), and acetyl-CoA acyltransferase 1a (ACAA1a), with ACAA1b functions as the major 3-keto-CoA thiolase B for the hydrolysis of DCA-CoA. Additionally, the rate of β-oxidation of DCAs decreases with short chain-length DCAs, suggesting a significant reason for the appearance of adipic (C6), sebacic (C10), and suberic (C8) DCAs in the urine [23-25]. Shorter chain DCAs are produced and transported into the cytosol, functioning as anaplerotic intermediates in metabolism [26]. One of the shorter-chain DCs that contribute to anaplerotic reactions is succinyl-CoA, which is converted by ACOT4 thiolase to succinate [27,28] that functions to replenish the TCA cycle and as a gluconeogenic metabolite [29]. Also, acetyl-CoA is converted by ACOT12 and ACOT8 thiolase to produce acetate [30,31] which can be used as an energy source in peripheral tissues or an anaplerotic metabolite for lipogenesis and cholesterol synthesis [1,32,33], resulting in increased Lipid Droplet (LD) formation in the liver [33,34], It will be interesting to determine whether fatty acid or DCA is the preferred source of acetate used in fatty acid synthesis and LD formation.

The ω and ω-1 oxidation of medium and long-chain fatty acids has received much interest since it has long been thought that activating this pathway in stressful conditions of fasting, diabetes, and high-fat diets prevents fatty acid toxicity. DCAs are potent uncouplers of mitochondrial respiration [35,36]. DCA increases in many mitochondrial FAO disorders where ω-oxidation and peroxisome β-oxidation increase DCA excretion [29]. This is a compensatory mechanism in which DCA metabolism by peroxisome β-oxidation produces anaplerotic metabolites, succinate, and acetyl-CoA, that increase the mitochondrial TCA cycle. Elevated cytosolic acetate from the metabolism of DCA increases fatty acid and cholesterol synthesis, leading to enhanced hepatic triglyceride synthesis and lipid droplet formation. Determining if saturated fatty acid or DCA-derived succinate and acetate induce changes in the epigenetic metabolic program will be important [37].

Both urinary and plasma levels of DCA increase in several disease states that include diabetes [38], MASLD [39], inborn error Fatty Acid Oxidation (FAO) defect [40,41], celiac disease [42], dicarboxylic aciduria [25], and Reye's syndrome [36]. In each of these conditions decreased mitochondrial oxidation is most likely compensated by the ω-hydroxylation and peroxisome β-oxidation of FAs. DCAs have been proposed as an alternative energy source in several disease states by providing anaplerotic intermediates of the TCA cycle. Oral administration of sebacic acid to Type II Diabetics (T2DM) improved glycemic control, improved insulin sensitivity, and reduced hepatic gluconeogenesis and glucose output. [43] In addition, dodecanedioic acid (C12-DCA) reduced muscle fatigue in T2DM patients. Recently, the hydroxylated C13-DCA, bempedoic acid, has been approved to lower LDL by inhibiting ATP-citrate lyase, reducing cholesterol and fatty acid synthesis (FAS), and activating AMP-protein Kinase (AMPK) to suppress gluconeogenesis and lipogenesis [44]. Administration of

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dodecanedioic acid DCA12 prevented acute kidney injury. Dietary 12-DCA reduced body fat, and fatty liver, and improved glucose tolerance in mice [45]. Increased levels of DCA are excreted in human urine under medium-chain triglyceride (MCT) feeding [25], which is used in the treatment of Alcohol-associated Liver Disease (ALD) [46] and as a nutritional supplement. Furthermore, in mice with hepatoblastoma, a deficiency of DCA catabolism with the administration of Dodecanedioic Acid (DDDA) led to hepatoblastoma necrosis and significantly longer survival than mice on standard diets [47].

Functional role of human CYP4 ω-hydroxylase in MASLD

A high-fat diet induces the ω-oxidation of fatty acids and increases the expression of *CYP4A11* in HepG2 human hepatoma cells [1,48]. RNA seq database analysis of patients with MASLD revealed increased *CYP4A11* and *CYP4A22* mRNA in steatosis and MASH [32]. In addition, the *CYP4F2* and *CYP4F3a* genes were increased in patients with steatosis, MASH, and cirrhosis. The CYP4F8 prostaglandin hydroxylase and *CYP4F11* mRNA levels increase in steatosis, MASH, and advanced hepatocellular carcinoma. In human patients, the *CYP4F12, CYP4F22*, and *CYP4V2* mRNA levels increase in steatosis and MASH, while the levels of *CYP4B1*, *CYP4X1*, and *CYPZ1* mRNAs decrease in steatosis and MASH [32] while the mRNA for these genes increases in HCC. In these RNA seq datasets, GSE13251 and GSE114564, GSE114564 and GSE 113564, PNPLA3 and MBOAT7 mRNA levels increase in steatosis, MASH, and advanced HCC. In contrast, mRNA levels of *CYP2E1* and *CYP3A4*, major drug metabolizing genes, decrease in steatosis, MASH, and HCC. These data indicate that members of the CYP4 gene family members contribute to the progression of MASLD through increased ω-hydroxylation of different chain-length FAs and bioactive eicosanoids. Fasting induces hepatic lipid accumulation through peroxisome β-oxidation of various DCAs [33], suggesting that increased lipolysis of these FAs elevates acetate levels, hepatic lipogenesis, and Lipid Droplet (LD) formation [1], leading to inflammatory MASH [49]. In human HepG2 cells, incubation with 1 mM FFA increased the expression of *CYP4A11* 3-fold and the levels of triglycerides 10-fold, leading to an elevation of 2.5-fold in Reactive Oxygen Species (ROS) and lipid peroxidation 3-fold [48]. Over-expression of *CYP4A11* increases expression of Tumor Necrosis Factor (TNF), Interleukin-1β (IL-1β), and interleukin 6 (IL-6) through activation of the NF-κβ signaling pathway. It will be essential to determine if the DCA levels increase and whether acetyl-CoA or acetate levels elevate since these latter molecules exhibit both anaplerotic and epigenetic effects on the progression of MASLD. It will be essential to determine if peroxisome compartmentalized acyl-CoA metabolism has a role in chromatin regulation [50] since it has recently been shown that ALDH1A3-acetaldehyde metabolism potentiates melanoma transcription heterogeneity [51,52].

In *Cyp4a14*-/- mice fed a high-fat diet, 20-HETE induces obesity and insulin resistance since the 20-HETE antagonist mediates [53], prevented hyperglycemia and hyperinsulinemia. In contrast, *Cyp4a14*$^{-/-}$ mice are resistant to hepatic steatosis and fibrosis, while Ad-*Cyp4a14* mice exhibited an increase in hepatic TG and LD formation due to enhanced uptake of fatty acid by elevated expression of CD36 [8]. Angiotensin II initiates renal fibrosis and increases *cyp4A14* expression mediated by the Mitogen-activated Protein Kinase (MAPK) pathway. *Cyp4a14*$^{-/-}$ mice are resistant to Ang II-induced renal fibrosis. Moreover, *Cyp4a14*$^{-/-}$ mice also resist bile duct ligation-induced cholestatic liver fibrosis [54]. Several of these studies attribute insulin resistance, obesity, and fibrosis to *Cyp4a14*-mediated increased production of 20-HETE. However, *Cyp4a14* p450 does not metabolize AA to 20-HETE [55]. The mouse has four major *Cyp4a isoforms, Cyp4A10, Cyp4A14*, and *Cyp4a12a*, male-specific, and *Cyp4a12b*, female-specific with five minor forms, including *Cyp4a29*, *Cyp4a30b, Cyp4a31, and Cyp4a32* [56]. *Cyp4a14*$^{-/-}$ mice exhibit increased plasma androgens. Androgen increases *Cyp4a12* expression in the kidney, increasing 20-HETE formation in kidney microsomes [9]. This compensatory increase in *Cyp4a12* P450 but not 4a10 P450 in *Cyp4a14*$^{-/-}$ mice further points to *Cyp4a12* P450's role in AA metabolism to 20-HETE. It will be important to determine if hepatic levels of 20-HETE increase in the *CYP4a14*$^{-/-}$ mice since *Cyp4a14*$^{-/-}$ female mice do not show an increase in *Cyp4A12* in kidney microsomes.

Functional role of *CYP2E1* in MASLD and alcohol-associated liver disease

Alcohol-induced MASLD progression is related to the amount and duration of alcohol consumption [57,58], with excessive alcohol consumption leading to an increase in *CYP2E1* activity, producing ROS causes Endoplasmic Reticulum (ER) stress and mitochondrial dysfunction that negatively inhibit FA oxidation [59]. *CYP2E1* contributes to oxidative stress and steatosis in chronic alcohol-exposure models and MASLD [40] by increasing lipid peroxidation and decreasing levels of antioxidants, superoxide dismutase, glutathione peroxidase, and aldehyde dehydrogenase, leading to elevated levels of protein carbonylation, nitration, phosphorylation and glycation that contribute to increased insulin resistance and impaired glucose tolerance [60]. *CYP2E1* P450 is a high-spin cytochrome that raises the redox potential and facilitates the generation of ROS [61,62] Despite using the P450 2E1 (*CYP2E1*) inducer isoniazid, there was no increase in F2-isoprostane production, the gold standard for ROS determination [63]. Also, the *Cyp2e1*$^{-/-}$ mice had similar levels of urinary isoprostanes as the wild-type animals, indicating that microsome *CYP2E1* induction by ethanol or isoniazid does not increase ROS [63]. However, mitochondrial *CYP2E1* did show enhanced isoprostane levels after ethanol treatment [64]. *CYP2E1* protein is found in both the endoplasmic reticulum and mitochondria. However, the role of the mitochondria in alcohol-associated or non-alcoholic MASLD is uncertain [64,65]. Similar to the ER-*CYP2E1*, the mt*CYP2E1* increases levels of ROS and mitochondrial 3-nitrotyrosine and 4-hydroxynonenal protein adducts and decreased mitochondrial aconitase activity and mitochondrial membrane potential [66]. The distribution of the *CYP2E1* in microsomes and mitochondria in the human liver may account for individual differences in ethanol toxicity and the initiation of alcohol-Associated Liver Disease (ALD) [67].

CYP2E1 P450 can ω-1 hydroxylate saturated and unsaturated fatty acids [10,68,69]. *CYP2E1* P450 metabolizes lauric and myristic acids to their respective ω-metabolites with turnover

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numbers of 3.8 and 2.4 min^{-1}, respectively, while *CYP4A11* P450 metabolizes lauric and myristic acid with turnover numbers of 7.3 and 2.1 min^{-1}, respectively [17]. *CYP2E1* and *CYP4A11* P450 bind lauric acid with similar Km values (5.8 and 4.7 µM, respectively), indicating competition in the metabolism of saturated fatty acid substrates. Both alcohol dehydrogenase ADH4 has a similar affinity for both ω and ω-1 hydroxylated fatty acids (ADH, Km 10-20 µM) in comparison to the oxidation of ethanol (2-40 mM), indicating that ethanol is not the physiological substrate for *CYP2E1* P450 under normal conditions. [70] In addition, aldehyde dehydrogenase (ALDH3A2, Km 4-19 µM) [71] confirms the importance of the ω and ω-1 pathways in the metabolism of fatty acids. RNA-seq database analysis revealed that *CYP2E1* expression is decreased during the progression of MASLD [32], suggesting that the level of 19-HETE decreases and 20-HETE increases. This indicates that the ω-hydroxylation pathway has a significant role in the progression of MASLD.

Liver Sinusoidal Endothelial Cells (LSECs) can metabolize ethanol, and ethanol can increase *CYP2E1* levels that produce acetaldehyde and acetyl-CoA, a substrate for protein acetylation and lipid synthesis. However, the *CYP2E1* ω-1 hydroxylation of fatty acid and peroxisomal β-oxidation would contribute to the acetyl-CoA pool. Ethanol increases heat shock protein 90 (Hsp90) acetylation and decreases its interaction with endothelial Nitric Oxide Synthetase (eNOS), resulting in decreased production of eNOS-derived Nitric Oxide (NO) [72]. The eNOS-derived NO-signaling [73] is a critical player in LSEC function through the activation of Vascular Endothelial Growth Factor (VEGF) that maintains LSEC fenestrae and prevents capillarization [74,75] The activity of eNOS is regulated by its interaction with several proteins, including the G-Coupled Protein Receptor (GCPR) β-Arrestin 2 and Hsp90. An increase in the acetyl-CoA pool results in Hsp90 acetylation, decreasing its interaction with eNOS and producing eNOS-derived NO [72]. Overexpression of the histone deacetylase 6 (HDAC6), which deacetylates Hsp90, increases the association of Hsp90 with eNOS, leading to elevated NO production [76]. Also, eNOS activity and NO production are enhanced by its interaction with β-arrestin-2 [77]. It is currently unknown to what extent the hepatocyte, LSEC microsome, mitochondrial *CYP2E1*, or its metabolites contribute to endothelial dysfunction in ALD and MASLD. Moreover, it will also be important to determine whether *CYP4* P450s are expressed in LSEC.

Role of *CYP4A11*- and *CYP2E1*-mediated fatty acid metabolism in MASLD

The synergistic role of *CYP2E1* and *CYP4A11* in the saturated and unsaturated fatty acids metabolism indicates their vital role in fasting, diabetes, and the progression of MASLD. Numerous studies have shown that *Cyp2e1*$^{-/-}$ knock-out mice are resistant to hepatic steatosis, steatohepatitis, and liver fibrosis by reducing fatty acid synthesis [78], decreasing ROS, and free radical production, hindering lipid peroxidation while increasing the expression of antioxidant genes and hepatic levels of glutathione [79,80] Both insulin resistance and hyperinsulinemia have a crucial role in hepatic fat accumulation and reflect common conditions of ALD and MASLD. *Cyp2e1*$^{-/-}$ mice are protected from high-fat-induced insulin resistance [60,81] with insulin, which is known to decrease *Cyp2E1* expression [82]. *Cyp2e1*$^{-/-}$ mice expressing the human *CYP2E1* transgene show increased hepatic steatosis, oxidative stress, insulin resistance, and liver injury [83]. It is unknown whether insulin resistance in MASLD increases *CYP2E1* by ketone bodies that stabilize *CYP2E1* P450 and prevent its degradation by the ubiquitin-dependent proteasome system.

The interplay of the *CYP2E1* and *CYP4* genes in steatohepatitis is evident in *Cyp2e1*$^{-/-}$ mice administered a methionine choline-deficient (MCD) diet as a model of MASLD. The *Cyp2e1*$^{-/-}$ mice neither prevented nor inhibited lipid peroxidation but induced an upregulation of the *Cyp4A10* and *Cyp4A14* genes [84], suggesting a synergistic relation between the *CYP2E1* and *CYP4A* genes in the progression of MASLD. In the obese db/db mice, inhibiting the *Cyp4A14* gene reduces ER stress, apoptosis, insulin resistance, and steatosis [85]. The *CYP4a14*$^{-/-}$ mice show attenuated hepatic steatosis and fibrosis [40.54]. Again, this reveals a close relationship between the *CYP2E1* and *CYP4A* genes in the progression of MASLD. It will be important to determine if hyperinsulinemia inhibits the expression of the *CYP2E1* gene and increases the expression of *CYP4A* genes in MASLD [86]. We analyzed the expression of the *CYP4A11*, *CYP4F2* and *CYP2E1* in patients with steatosis, steatohepatitis, cirrhosis, and HCC and found that both *CYP4A11* mRNA and protein increase in the progression of MASLD [52], while *CYP4F2*, the primary P450 in the metabolism of AA to produce 20-HETE, decreases in MASLD progression.

An opposing role of *CYP4A11* and *CYP2E1* in the metabolism of arachidonic acid

Both the *CYP2E1* and *Cyp4A14* genes are synergistically regulated by the nuclear transcription factor erythroid factor 2 (NRF2) during fasting, diabetes, high-fat diet, and ethanol intoxication [87,88]. NRF2 activates several antioxidant genes [89] and Nrf2$^{-/-}$ mice display increased high-fat-induced steatosis and steatohepatitis [90]. *Cyp2e1*$^{-/-}$ and *Cyp4a14*$^{-/-}$ mice resist high-fat diet-induced liver damage [8]. The observation that *Cyp2e1*$^{-/-}$ mice fed an MCD diet have severe steatohepatitis with increased *Cyp4a10* and *Cyp4a14* suggests a relationship between these genes in MASLD progression. High-fat diet-induced obesity and insulin resistance in *CYP4a14*$^{-/-}$ mice are believed to be due to increased expression of the *Cyp4a12a* gene that produces the vasoconstrictive 20-HETE. In the *Cyp2e1*$^{-/-}$ mice fed the MCD diet, there was no increase in *Cyp4a12a* mRNA [84], indicating a complex synergistic or opposing role of the *CYP4A* and *CYP2E1* genes at different stages of MASLD.

The increased expression of the *CYP2E1* and *CYP4A11* genes in steatosis, with a down-regulation of the *CYP2E1* P450 and elevated *CYP4A11* in the progression of MASLD indicate the differential role of these genes. Both *CYP2E1* and *CYP4A11* proteins metabolize AA to 19-Hydroxyeicosatetraenoic Acid (19-HETE) and 20-hydroxyeicosatetraenoic acid (20-HETE), respectively, with 19-HETE having a vasodilatory effect and 20-HETE a vasoconstrictive eicosanoid [10,91,92] The 20-HETE eicosanoid is a critical player in influencing the sensitivity of

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the vasculature to constrictor stimuli, regulating endothelial function, influencing the renin-angiotensin system (RAS), a driver of vascular remodeling independent of blood pressure elevations, and the migration and proliferation of certain liver cells as well as metabolic syndrome and liver fibrosis [93,94,95] Mice fed a high-fat diet showed significantly higher 20-HETE/EET+DHET formation in the liver, indicating a role in the progression of metabolic syndrome [96]. In contrast, the role of *CYP2E1* in producing19-HETE in MASLD is unknown although 19-HETE protects cardiomyocytes from hypertrophy, promotes smooth muscle relaxation, and is believed to antagonize the effects of 20-HETE [97,98]. *CYP4a11* P450 has a Km of 228 µM for AA, a turnover number of 49.8 min^{-1}, and a catalytic efficiency of 0.21 M^{-1} sec^{-1} [99]. In contrast, *CYP2E1* P450 has a Km of 62 µM for AA with a turnover number of 0.08 min^{-1} with a catalytic efficiency of 0.0013 M^{-1} sec^{-1}, indicating the AA is metabolized to 20-HETE over *CYP2E1* synthesis of 19-HETE [10,100].

Both 19-HETE and 20-HETE bind specific receptors to initiate their biological effects. The 19-HETE induces vasorelaxation and inhibition of platelet activation by activating the prostacyclin (IP) receptor [91]. In contrast, 20-HETE initiates its biological effects by activating the GPR75 receptor [2,3,101]. (Figure 2). The opposing roles of *CYP2E1* 19-HETE and *CYP4A11* 20-HETE are apparent from 19-HETE's antagonism of 20-HETE-induced vascular sensitization and hypertension [97], inhibition of the Na^+/K^+-ATPase [102,103] and functions to increase volume absorption in renal proximal tubules [102]. These effects are modulated by the inositol phosphate (IP) receptor coupled Gαs-mediated protein kinase A (PKA) activation that increases cAMP levels [11]. In contrast, the 20-HETE activation of the GPR75 receptor causes opposing biological effects compared to the 19-HETE-IP receptor. Activation of the GPR75 receptor by 20-HETE stimulates Gαq/11 dissociation, accumulation of IP, and binding of GPRC-Kinase Interacting Protein-1 (GIT1) that facilitates Src transactivation of endothelial EGFR [3]. Activation of endothelial EGFR by GPR75 stimulates the MAPK pathway, resulting in NF-κβ activation [2] of Angiotensin-Converting Enzyme (ACE) and the uncoupling of eNOS.

The 20-HETE/GPR75 activation of the NF-κβ pathway and suppression of endothelial eNOS have important implications for autocrine signaling in sinusoidal homeostasis in CLD, from portal hypertension to vascular thrombosis. Suppression of eNOS leads to capillarization (development of basement membrane) of the Liver Sinusoidal Endothelial Cell (LSEC) accompanied by increased vasoconstrictors, proinflammatory, profibrotic, and prothrombic factors [104,105]. NO has an anti-fibrotic role in LSEC mediated by the VEGF pathway, which is diminished by capillarization [73]. *CYP4A11*-mediated production of 20-HETE induces hepatic fibrosis via activating the TGF-β1/Smad signaling pathway [4]. Endothelial eNOS is critical to CLD [106]. 20-HETE mediated increase in plasma level of angiotensin-II is significantly elevated in patients with liver cirrhosis and is found to be a critical factor in inducing portal hypertension [75,107]. Furthermore, angiotensin-II also induces the proliferation of hepatic stellate cells, increases

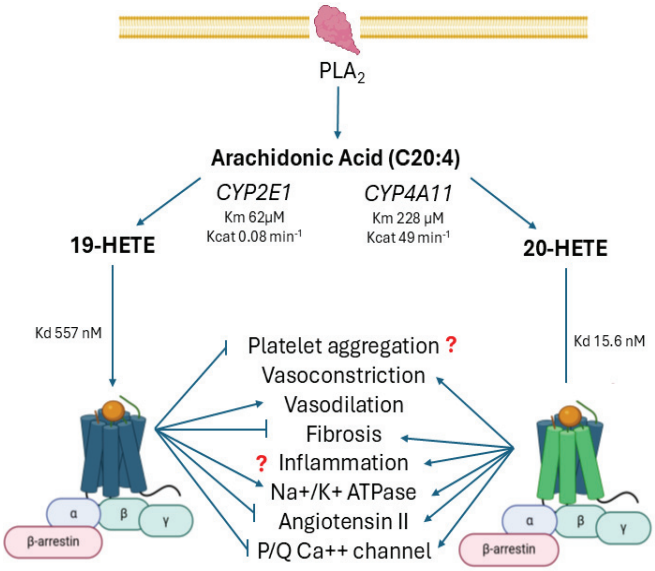

Figure 2: The opposing role of P4502E1 19-HETE and P4504A11 20-HETE in regulating physiological processes. During stress or inflammation, Phospholipase A2 (PLA2) releases Arachidonic Acid (AA) from membrane phospholipids. Arachidonic acid is metabolized by P4504A11 to 20-HETE or 19-HETE by P4502E1. P4502E1 has a low Km for AA (62 µM) than P4504A11 (228 µM), but P4504A11 has a high Kcat 49 min-1 than P4502E1 kcat 0.08 min-1. However, P4502E1 makes up 6% of human microsome P450 while P4504A11 represents only 1%. The prostacyclin (IP) receptor has a lower affinity for 19-HETE (Kd 567nM) than GPR75 affinity for 20-HETE (15.5 nM). The CYP2E1 or CYP4A11 P450 level and their induction by ethanol or fatty acids determine which pathway becomes more active in Chronic Liver Disease (CLD).

the mRNA level of TGF-β1 and collagen-I, and stimulates the formation of the Extracellular Matrix (ECM) [108,109] It has been shown that patients with liver cirrhosis excrete high levels of 20-HETE [110,111] It is known that 20-HETE is a weak, Cyclooxygenase (COX)-dependent vasoconstrictor of the portal circulation, and it was supposed to be involved in the pathophysiology of portal hypertension [111,112] In addition, 20-HETE was found to be involved in abnormalities related to liver diseases, particularly cirrhosis [112]. It is unknown whether 20-HETE or COX2-mediated metabolism of 20-HETE to 20-hydroxy PGH2 mediates the effects of 20-HETE in liver cirrhosis [113]. However, combined therapy with a COX2 and 20-HETE inhibitor reduces colon tumor growth, suggesting a synergistic relationship between 20-HETE and prostanoids [114]. Interestingly, MC38 colon tumor-bearing mice treated with the COX2 inhibitor Rofecoxib had increased plasma levels of 20-HETE with no increase in CYP4a expression. Elevated 20-HETE induces phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and cyclin D-1/2, suggesting that increased 20-HETE would increase cell proliferation, as seen in MC38 colorectal cells. However, treatment with Rofecoxib and CYP4 inhibitor HET0016 dramatically decreased cell proliferation. These results suggest that 20-HETE has a pivotal role in undefined cell proliferation [115]. Over 50% - 75% of AA-produced metabolites are 19-HETE and 20-HETE [116], with 20-HETE a COX-dependent vasoconstrictor of portal circulation in portal hypertension [111,112], while 11,12-EET was a vasoconstrictor in the porto-sinusoidal circulation, but functions as a vasodilator of mesenteric arterial vessels. These results suggest that 20-HETE or 20-PGG_2/PGH_2 causes

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portal vein vasoconstriction while EET induces vasodilation of mesenteric arteries resulting in increased blood flow and portal hypertension in cirrhosis. Several studies have suggested that inhibition of COX1/2 attenuates the vasoconstrictive properties of 20-HETE [113]. It has also been shown that 20-OH-PGE_2 enhances adipocyte hypertrophy, leading to dysfunctional adipogenesis [117]. It is unknown whether 20-HETE or the metabolism of 20-HETE by either COX1 or COX2 to 20-PGG_2/PGH_2 have divergent effects on portal hypertension. The 20-HETE-producing cytochrome P450s are up-regulated in human cancer [118] and induce mitogenic and angiogenic responses. Combination therapies for HCC with celecoxib and sorafenib enhanced growth inhibition [119,120], and celecoxib with a tyrosine kinase inhibitor decreased proliferation and angiogenesis in HCT colon cancer cells [121]. It will be critical to determine the functional roles of 20-HETE and 20-OH PGG_2/PGH_2 in portal hypertension and progression of MASLD.

Physiological role of 20-HETE and 19-HETE in disease states

The opposing autocrine and paracrine roles of 20-HETE and 19-HETE in the regulation of metabolism are evident by high-fat diet-mediated *SREBP-1a* induction of *CYP4F2* [122] that produces 20-HETE, which increases insulin secretion [11,91], leading to suppression of the *CYP2E1* [82]. Increased 20-HETE impairs insulin signaling, and its effect requires activating its receptor GPR75. In contrast, hepatocyte-specific overexpression of *CYP2E1* increased hepatic oxidative stress in the liver, fasting insulin, and histological liver damage [83]. *CYP2E1* overexpression reduced hepatic insulin signaling, decreased glycogen storage, and increased glucose synthesis. *CYP2E1* hepatic overexpression increased oxidative stress, increased systemic insulin resistance, decreased insulin signaling in the liver, and increased hepatic fat accumulation. Elevated 20-HETE contributes to HFD-induced obesity, insulin resistance, and impaired insulin signaling [53]. In contrast, Isoniazid induction of *Cyp2E1* decreased both *Cyp4A* and 20-HETE levels with an increase in 19-HETE [123]. Triple siRNA lipid nanoparticles (LNPs) targeting *Cyp2e1*, *Cyp4a10*, and *Cyp4a14* significantly ameliorated chronic alcohol-associated liver injury [124].

Differential ethanol metabolism by fatty acid hydroxylase metabolites

Ethanol impacts mitochondrial and peroxisomal β-oxidation of fatty acids and ω- and ω-1 hydroxylation of eicosanoids. Ethanol metabolism by Alcohol Dehydrogenase (ADH) increases the NADH/NAD^+ ratio, inhibiting mitochondrial β-oxidation and contributing to alcohol-associated steatosis development. ADH has a lower Km for oxidation of hydroxylated fatty acid (10-40 μM) than for the oxidation of ethanol (Km 0.2-2 mM), indicating that high ethanol concentration (5.6 mM) will inhibit the oxidation of hydroxylated fatty acids [70]. In contrast, 17 μM ω-hydroxylated stearic acid inhibits oxidation of ethanol by ADH. Ethanol feeding increased fatty acid ω-oxidation in response to ethanol inhibition of mitochondrial β-oxidation [125]. *CYP2E1* has a higher Km for ethanol (8-10 mM) than ADH (0.2-2 mM) and thus metabolizes only 10% of body ethanol. Interestingly, rats fed a Lieber-DeCarli liquid ethanol diet supplemented with long-chain polyunsaturated fatty acid (PUFA) developed severe liver injury. In contrast, if the ethanol liquid diets were supplemented with medium-chain triglycerides, these rats displayed a normal liver [126]. Binge drinking induces adipose tissue lipolysis, increasing circulating free fatty acid (FFA) and enhancing *CYP2E1* activity, resulting in acute liver injury [127]. The synergistic effects of ethanol and increased serum fatty acid may be one mechanism of *CYP2E1*'s role in MASLD. In obese people with MASLD, increased *CYP2E1* protein content and activity correlated with the development of liver injury [128]. This contrasts the RNA-seq database analysis, in which *CYP2E1* mRNA decreased in MASH and levels dropped significantly in HCC. This difference may be due to increased serum FFAs in obese individuals compared to normal individuals with MASLD. Determining *CYP2E1* mRNA and protein levels at different stages of MASLD progression and *CYP2E1* activity will be necessary.

CYP2E1 makes up 6.6% of total hepatic P450, while *CYP4A11* is less than 1% of total hepatic P450 under basal conditions [129], but their levels could be elevated by ethanol intake, ketone bodies, or fasting. It is apparent that the substrate, saturated fatty acid or arachidonic acid, and diet, high-fat or alcohol, determine the importance of *CYP2E1* ω-1 or *CYP4A11* ω-hydroxylation of these substrates in CLD. Liver disease induces macrovascular and microvascular events that result in microthrombi in the hepatic venules [130]. In cirrhotic patients, these microthrombi cause parenchymal extinction [131]. Microthrombi and parenchymal injury disrupt normal hepatic blood flow, causing hepatocyte apoptosis, which is replaced by fibrotic septa [132]. The recent observation that lung fibroblasts produce prostacyclin, which contributes to antithrombotic protection and blocks fibrosis, is a new paradigm [12]. It will be important to determine if *CYP2E1* 19-HETE activation of the prostacyclin receptor (IP) is protective in liver fibrosis and prevention of chronic liver disease progression.

Conclusion

Chronic liver disease is characterized by portal hypertension, which is a driver of cirrhosis, ascites, gastro-esophageal varices, hepatorenal syndrome, hypersplenism, and hepatic encephalopathy due to portosystemic shunting. A large number of patients with portal hypertension have few therapeutic options. Currently, non-selective beta-blockers (NSBB) target the decrease of splanchnic venous inflow and cardiac output by blocking the β1-adrenergic receptor (β1-AR) and inducing vasoconstriction in the splanchnic region by blocking β2-AR. Unfortunately, NSBBs decrease portal pressure by only 15%, indicating that new therapies are still needed.

The *CYP4A11* ω-hydroxylase and the *CYP2E1* ω-1 hydroxylase have synergistic roles in the metabolism of saturated and unsaturated fatty acids during fasting or fatty acid overload in obesity and diabetes. Nuclear Erythroid Factor 2 (Nrf2) regulates the *CYP4A11* and *CYP2E1* genes during the stress response to fatty acids. The hydroxylation of fatty acids by ω and ω-1 hydroxylases and peroxisomal β-oxidation results in the production of succinate for gluconeogenesis and acetyl-

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CoA that can serve as a substrate for cholesterol and fatty acid synthesis, increasing lipogenesis and Lipid Droplet (LD) formation in the liver that results in steatosis. With the initiation of excess lipids in the liver, hepatitis ensues, and an inflammatory response results in the activation of phospholipase A2 and the release of Arachidonic Acid (AA). AA is ω-hydroxylated by *CYP4A11* and ω-1 hydroxylated by *CYP2E1*, producing 20-HETE and 19-HETE, respectively, that have opposing physiological roles in the progression of MASLD with *CYP4A11*-mediated 20-HETE vasoconstrictor activates the GPR75 receptor, which initiates inflammation and divergent un-characterized roles in the progression of MASLD. In contrast to the *CYP4A11*-mediated 20-HETE production, the *CYP2E1*-related ω-1 arachidonic acid metabolite 19-HETE is a vasodilator by activating the prostacyclin receptor, which opposes the vasoconstrictor function of 20-HETE. The decrease in *CYP2E1* during the progression of MASLD, as revealed by RNA-seq database analysis, suggests that the level of 19-HETE would decrease while the pro-lipogenic and inflammatory 20-HETE increases.

Many issues need to be addressed before determining the roles of the *CYP4A11*-mediated 20-HETE and *CYP2E1*-related 19-HETE in steatosis, steatohepatitis, cirrhosis, and HCC, and possible therapeutic targets in the treatment of CLD. Among these issues, 1) 19-HETE level needs to be determined during the progression of MASLD; 2) inhibition of COX1/2 seems to ameliorate the function of 20-HETE and thus the physiological role of 20-OH PGG_2/PGH_2 or 20-OH PGE_2 needs to be determined; 3) what role does DCA play in the progression of MASLD, and 4) Can inhibition of the 20-HETE/GPR75 and activation of the 19-HETE/IP2 delay MASLD progression and be a therapeutic option in the treatment of portal hypertension in cirrhosis.

Author contributions

JPH: conceptualization, writing drafts, revisions, and overall supervision; VG, critical data analysis, suggestions, and manuscript revisions.

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