Review

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Atypical functions of xenobiotic receptors in lipid and glucose metabolism

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Abstract: Xenobiotic receptors are traditionally defined as xenobiotic chemical-sensing receptors, the activation of which transcriptionally regulates the expression of enzymes and transporters involved in the metabolism and disposition of xenobiotics. Emerging evidence suggests that "xenobiotic receptors" also have diverse endobiotic functions, including their effects on lipid metabolism and energy metabolism. Dyslipidemia is a major risk factor for cardiovascular disease, diabetes, obesity, metabolic syndrome, stroke, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH). Understanding the molecular mechanism by which transcriptional factors, including the xenobiotic receptors, regulate lipid homeostasis will help to develop preventive and therapeutic approaches. This review describes recent advances in our understanding the atypical roles of three xenobiotic receptors: aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and constitutive androstane receptor (CAR), in metabolic disorders, with a particular focus on their effects on lipid and glucose metabolism. Collectively, the literatures suggest the potential values of AhR, PXR and CAR as therapeutic targets for the treatment of NAFLD, NASH, obesity and diabetes, and cardiovascular diseases.

Keywords: aryl hydrocarbon receptor; constitutive androstane receptor; lipid metabolism; pregnane X receptor; xenobiotic receptors.

Introduction

As developing countries adopt Western diets, obesity superseded malnutrition as a leading public health issue worldwide [1]. Nearly a quarter of the world's adults currently live with metabolic syndrome, and it is becoming more common due to a rise in obesity [2]. Despite the advances in hyperlipidemia therapies, in particular by the lipid-lowering drug statins, patients with these diseases continue to have high morbidity and mortality [3–5]. Dyslipidemia refers to a cluster of abnormalities of plasma lipids and lipoproteins, including hypertriglyceridemia, low serum high-density lipoprotein (HDL) level, and high low-density lipoprotein (LDL) levels [6, 7]. The pathological factors for dyslipidemia are complex and these factors and pathways are often inter-dependent and 'cross-regulated'. Increased free fatty acid and lipid accumulation in certain organs or tissues drive a primary defect in energy balance that produces obesity, which also results in pro-thrombotic and pro-inflammatory states [4]. Furthermore, as the incidence of diabetes mellitus increased, the link between dyslipidemia and insulin resistance has been recognized. Therefore, a single agent that targets one or two aspects of lipid metabolism is not likely to prevail, and more comprehensive approaches for lipid management with pleiotropic health benefits are eagerly needed. To develop new therapies, we must have a deeper understanding of the genetic and transcriptional control of lipid metabolism at a molecular level [4].

Overview of lipid metabolism

Fatty acid and triglyceride metabolism

Liver is the hub of fatty acid synthesis and triglyceride storage. Liver integrates incoming signals to control triglyceride production for use by other tissues and for storage in adipose tissues. Triglycerides are the preferred storage nutrient to buffer against fluctuations in energy demands and availability. Hepatic steatosis, or fatty liver, is defined as the presence of cytoplasmic triglyceride

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droplets in more than 5% of hepatocytes [8]. Fatty liver is commonly associated with metabolic syndromes including obesity and type 2 diabetes and can lead to inflammation, fibrosis, and even cirrhosis and cancer.

Steatosis may develop as a consequence of multiple dysfunctions. The fatty acids used for hepatic triglyceride formation are originated from *de novo* synthesis, diet, and adipose tissue. Carbohydrate feeding promotes *de novo* lipogenesis by inducing the key enzymes involved in this pathway such as the fatty acid synthase (FAS), stearoyl CoA desaturase 1 (SCD-1), and acetyl coenzyme A carboxylase 1 (ACC-1), all of which are under the transcriptional control of the master lipogenic transcriptional factor sterol response element binding protein-1c (SREBP-1c). Lipoprotein lipase (LPL) and adipocyte triglyceride hydrolase (ATGL) catalyze the hydrolysis of the triglyceride in the chylomicrons and adipocytes, respectively; thereby releasing free fatty acids into the circulation. The liver takes up free fatty acids via the fatty acid transport protein (FATP) or fatty acid translocase (FAT/CD36) when there is an excess of circulating fatty acids. Once in the liver, fatty acids can be oxidized to produce energy and ketone bodies, re-esterified to triglyceride, or exported as very-low-density lipoproteins (VLDL). Carnitine palmitoyltransferase 1 (CPT1) and mitochondrial 3-hydroxy-3-methylglutarate-CoA synthase (HMGCS) are two key enzymes in β-oxidation and ketogenesis. Apolipoprotein B100 (ApoB100) is the key component that controls the overall rate of VLDL production and secretion [9]. In summary, steatosis may arise from an imbalance between triglyceride acquisition and removal due to increased fatty acid synthesis and uptake, decreased fatty acid β-oxidation, and reduced triglyceride secretion (Figure 1).

Cholesterol and lipoprotein metabolism

Cholesterol and the associated lipoprotein disorders are risk factors for coronary artery disease. The association between LDL and VLDL and coronary artery disease has been supported by large-scale epidemiological studies [10]. Upon ingestion, dietary fats are emulsified and packaged into very large lipoproteins, the chylomicrons, in the intestinal epithelium and transported via intestinal lymph to the liver, where the lipids are further processed. Both cholesterol and triglycerides are packaged into VLDL, which contains ApoB as their main lipoprotein, and then are exported to the periphery. In the circulation, LPL, lecithin-cholesterol acetyltransferase (LCAT), and LDL receptor (LDLR) located on the membrane surface mediate the endocytosis and complete the transport of triglycerides and cholesterol to target tissues. This process is referred to as forward cholesterol transport (FCT) [11] (Figure 2).

Reverse cholesterol transport (RCT) is a process responsible for the removal of excess cholesterol from peripheral tissues and it accounts for the return of the cholesterol to the liver [12]. HDL is believed to play a key role in this pathway and the level of HDL is strongly and inversely correlated with the risk for atherosclerosis [13]. The process of HDL maturation begins with the secretion of lipid-poor apoA-I and nascent discoid-like HDL particles (preβ-HDL) by the liver and intestine, followed by acquisition of cholesterol and phospholipids efflux mediated by the ATP-binding cassette (ABC) transporter family of membrane proteins, especially ABCA1. Cholesterol carried by HDL further undergoes remodeling via the enzyme LCAT. These mature HDL particles can either transport cholesterol from HDL to the liver via the scavenge receptor B-I (SR-BI), or exchange cholesterol and triglycerides between ApoB-containing particles VLDL and LDL through the action of cholesteryl ester transfer protein (CETP) [11, 14]. Once in the liver, cholesterol may be targeted for conversion into bile acids through the enzymatic action of cholesterol 7α-hydroxylase (CYP7A1), or direct biliary excretion via the heterodimer transporter pair ABCG5/8. Biliary cholesterol secretion is regarded as the final step for the elimination of cholesterol and is crucial for regulating daily cholesterol levels in the bloodstream [15] (Figure 2).

Xenobiotic receptors as master regulators of xenobiotic metabolism

Exposures to xenobiotics such as environmental chemicals and drugs have a profound influence on human health. The induction of xenobiotic metabolizing enzyme genes in response to chemical insults is an adaptive response found in most organisms. The detoxification and clearance of these xenobiotics are accomplished by the concerted action of Phase I cytochrome P450 (CYP) enzymes, Phase II conjugating enzymes, and drug transporters [16]. The P450 enzymes catalyze the monooxygenase reactions of lipophilic compounds facilitated by the reducing power of the NADPH P450 oxidoreductase [17, 18]. Phase II enzymes are several large group of transferases, such as sulfotransferase (SULT), glutathione *S*-transferase (GST), and UDP-glucuronosyltransferase (UGT), which conjugate polar functional groups onto xenobiotics [19]. Finally, the members of ABC transporter proteins and solute carrier

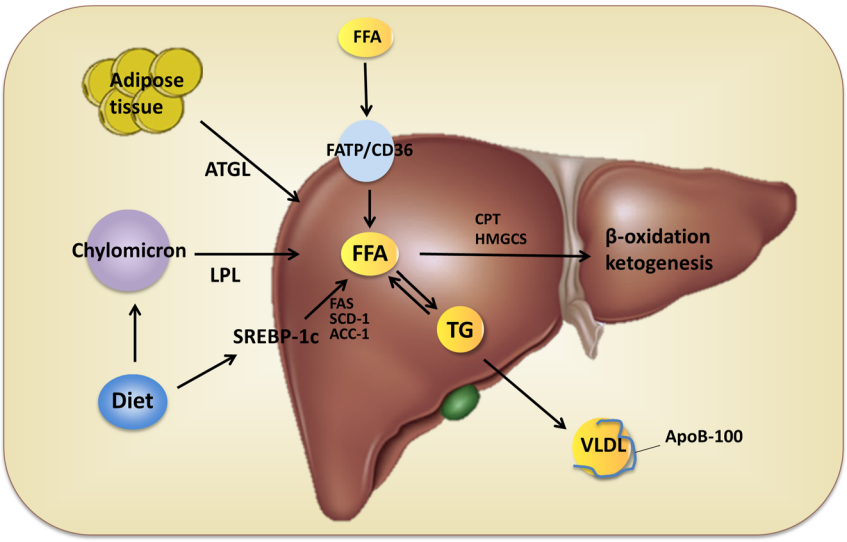

Figure 1: Summary of fatty acid and triglyceride metabolism in the liver. The fatty acids are originated from *de novo* synthesis, diet, or adipose tissue. LPL and ATGL catalyze the hydrolysis of the triglyceride in the chylomicrons and adipocytes. Carbohydrate feeding promotes *de novo* lipogenesis by inducing the key enzymes FAS, SCD-1, and ACC-1 through the master lipogenic transcriptional factor SREBP-1c. FATP or FAT/CD36 can also take up circulating fatty acids into the liver. Liver fatty acids can be oxidized in mitochondria to produce energy and ketone bodies by CPT and HMGCS, or re-esterified to TG and exported as VLDL. Increased fatty acid synthesis and uptake or decreased fatty acid β-oxidation and triglyceride secretion may cause hepatic steatosis. FFA, free fatty acid; LPL, lipoprotein lipase; ATGL, adipocyte triglyceride hydrolase; FAS, fatty acid synthase; SCD-1, stearoyl CoA desaturase 1; ACC-1, acetyl coenzyme A carboxylase 1; SREBP-1c, sterol response element binding protein-1c; FATP, Fatty acid transport protein; FAT/CD36, fatty acid translocase; CPT, carnitine palmitoyl transferase; HMGCS, 3-hydroxy-3-methylglutaryl-CoA synthase; TG, triglyceride; VLDL, very-low-density lipoproteins.

family act to mediate the excretion process [20]. Although in most cases, the biotransformation of xenobiotics leads to pharmacologically inactive metabolites, it may also activate so-called pro-drugs to pharmacologically active products or even to toxic metabolites [21].

Most drug-metabolizing enzymes are inducible in response to xenobiotics [22, 23]. However, the molecular basis underlying this drug-induced metabolism remained largely unknown for a long time. Discovery of xenobiotic receptors stemmed from the concept that xenobiotic induction was mediated by a receptor through a transcriptional machinery, which is the so called "induction-receptor" hypothesis. The plausibility of this hypothesis took a great leap forward with the discovery of the dioxin receptor or the aryl hydrocarbon receptor (AhR) in 1976 [24]. AhR is a ligand-activated transcription factor that belongs to the basic helix–loop–helix (bHLH)/Per-Arnt-Sim (PAS) family [25]. Upon binding to its agonists, such as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) or 3-methylcholanthrene (3-MC), AhR dissociates from its cytoplasmic complex and translocates into the nucleus, forms heterodimers with its partner AhR nuclear translocator (Arnt), binds to dioxin response elements (DREs) located in the promoter of its target genes, and activates the transcription (Figure 3). Examples of AhR target genes include Phase I CYP1As and CYP1B1, Phase II UGT1As, and TCDD-inducible poly (ADP-ribose) polymerase (TiPARP) [23, 26]. The evidence that AhR knockout mice showed impairment in normal development of the liver, immune system, heart, and vascular tissues suggested the existence of endogenous physiological AhR ligands as well as its biological function beyond mediating xenobiotic metabolism [27–30]. In recent years, several endogenous AhR ligands have been found, including tetrapyroles, arachidonic acid metabolites, tryptophan catabolite, and modified LDL [27, 31, 32].

Compared to AhR whose discovery preceded the era of receptor cloning and resulted from efforts to understand the mechanism of TCDD-induced drug metabolizing enzymes, the xenobiotic nuclear receptors pregnane X receptor (PXR, NR1I2) and constitutive androstane receptor (CAR, NR1I3) were discovered as "orphan receptors" without knowing their ligands and functions [33]. PXR and CAR share several important characteristics of xenobiotic receptors. They are expressed predominantly in the liver and small intestine where their target genes are located and

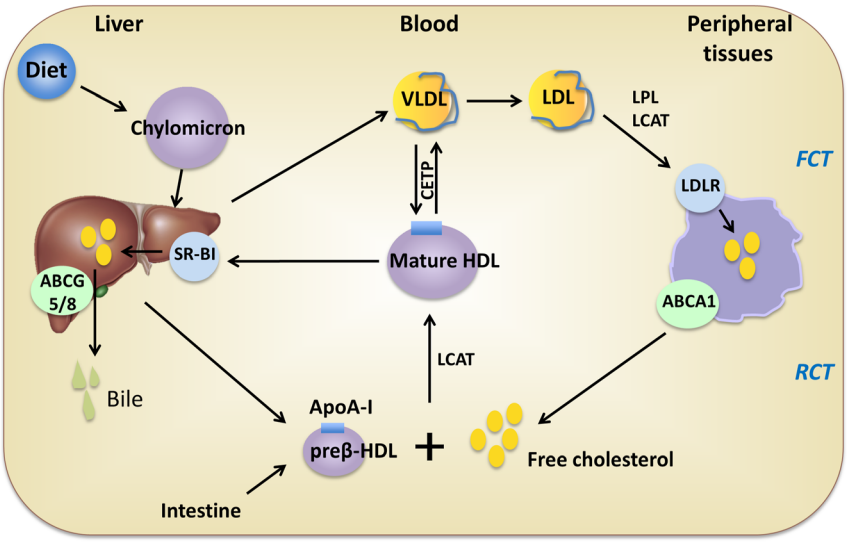

Figure 2: Overview of cholesterol and lipoprotein metabolism. FCT is the transporter of triglycerides and cholesterol to peripheral tissues. Dietary fats and cholesterol are transported to the liver by chylomicrons. The liver packages cholesterol and triglycerides into VLDL and VLDL is exported to the periphery with the help of LPL, LCAT, and LDLR. RCT is a process for the recycling of cholesterol from periphery tissues back to the liver. The process of HDL maturation begins with the secretion of lipid-poor apoA-I and nascent discoid-like HDL particles by the liver and intestine, followed by acquisition of cholesterol and phospholipids efflux mediated by the ATP-binding cassette transporter family member ABCA1. Cholesterol carried by is HDL matured by LCAT and taken up into the liver via SR-BI or redistributed to the apo-B containing particles VLDL and LDL through the action of CETP. Cholesterol in the liver can be excreted directly into bile via the ABCG5/8. FCT, forward cholesterol transport; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein; LCAT, lecithincholesterol acetyltransferase; LDLR, LDL receptor; RCT, reverse cholesterol transport; HDL, high-density lipoprotein; ABC, ATP-binding cassette; SR-BI, scavenge receptor B-I; CETP, cholesteryl ester transfer protein; ABCG5/8, ATP-binding cassette sub-family G member 5/8.

are capable of binding to a wide variety of structurally diverse chemicals including endogenous and synthetic steroids, pharmaceutical agents, and xenobiotic chemicals. Similar to AhR, PXR and CAR are nucleo-cytoplasmic shuttling proteins, and both subcellular compartmentalization and intracellular trafficking are crucial in their transcriptional functions. Upon ligand binding, PXR and CAR form heterodimers with the retinoid X receptor (RXR) and trigger the transcription of target genes (Figure 3). PXR and CAR not only show an overlap in their ligands, but also share many target genes including Phase I Phase II enzymes and drug transporters [34, 35]. In addition, PXR and CAR have also been proposed to have numerous endobiotic functions by regulating genes involved in the metabolism of endobiotics including bilirubin, bile acids, and steroid hormones [36]. Of note, there are marked species differences in the ligand-dependent activation of PXR and CAR, which is attributed to the sequence divergence in their ligand-binding domains. For instance, pregnenolone-16α-carbonitrile (PCN), a synthetic antiglucocorticoid, is a potent agonist for the mouse and rat PXR but has little effect on the human and rabbit PXR. Conversely, rifampicin, a macrolide antibiotic, activates human and rabbit PXR, but has little effect on rat and mouse receptors [37]. Similarly, 1,4-Bis (2-[3,5-dichloropyridyloxy]) benzene (TCPOBOP), a potent mouse CAR ligand, cannot activate either rat or human CAR, whereas, androstanol represses mouse but not human CAR [38]. The creation of PXR and CAR null mice [39–41] as well as the PXR and CAR humanized mice [39, 42] has made it possible to address the species specificity of xenobiotic responses *in vivo*.

Xenobiotic receptors in lipid and glucose metabolism

While AhR, PXR, and CAR were initially characterized as xenobiotic receptors, subsequent observations have pointed to their equally important endobiotic functions. More recent studies suggested these xenobiotic receptors play many other essential biological functions, such as AhR affecting the expansion of human hematopoietic stem

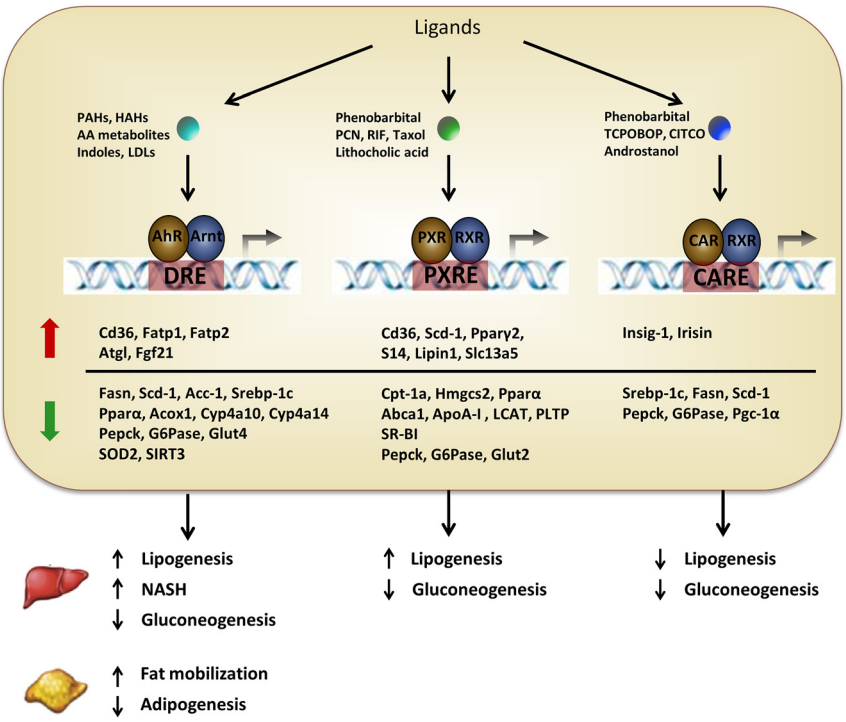

Figure 3: Summary of the major responsive genes of AhR, PXR, and CAR involved in lipid and glucose metabolism. Both xenobiotics and endobiotics can activate the AhR-Arnt, PXR-RXR, and CAR-RXR functional heterodimers, which bind to a DRE, PXRE, or CARE within the promoter region of target genes. This binding results in the regulation of gene expression. Note that the listed target genes that are either up-or down-regulated here are not complete and not intended to specify a particular cell type. PAHs, polycyclic aromatic hydrocarbons; HAHs, halogenated aromatic hydrocarbons; AA, amino acids; LDLs, low-density lipoprotein; PCN, pregnenolone-16α-carbonitrile; RIF, rifampicin; TCPOBOP, 1,4-Bis (2-[3,5-dichloropyridyloxy]) benzene; CITCO, 6-(4-chlorophenyl) imidazo [2, 1-b] [1, 3] thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl) oxime. Fatp, fatty acid transport protein; Atgl, adipocyte triglyceride hydrolase; Fgf21, fibroblast growth factor 21; Fasn, fatty acid synthase; Scd-1, stearoyl CoA desaturase 1; Acc-1, acetyl coenzyme A carboxylase 1; Srebp-1c, sterol response element binding protein-1c; Pparα, peroxisome proliferator-activated receptor α; Acox1, Acyl-CoA Oxidase 1; Pepck, phosphoenolpyruvate carboxykinase; G6Pase, glucose 6-phosphatase; Glut4, glucose transporter 4; SOD2, superoxide dismutase 2; SIRT3, sirtuin deacetylase 3; Pparγ2, peroxisome proliferator-activated receptor γ2; S14, thyroid hormone responsive spot 14 protein; Cpt-1a, carnitine palmitoyltransferase 1a; Hmgcs2, 3-hydroxy-3-methylglutarate-CoA synthase; Abca1, ATP-binding cassette transporter family member A1; LCAT, lecithin-cholesterol acetyltransferase; PLTP, phospholipid transfer protein; SR-BI, scavenge receptor B-I; Glut2, glucose transporter 2; Pgc-1α, peroxisome proliferative activated receptor-γ co-activator 1α; AhR, aryl hydrocarbon receptor; PXR, pregnane X receptor; CAR, constitutive androstane receptor; DRE, dioxin response element; PXRE, PXR response element; CARE, CAR response element; ABC, ATP-binding cassette.

cells [43] and regulating antibacterial defense [44], PXR regulating gastrointestinal barrier function [45] and inhibiting hepatic stellate cell trans-differentiation [46], and CAR interacting with proteasome [47, 48].

A large body of evidence has shown these receptors also function as metabolic sensors. They play vital roles in responding to the presence of endogenous and exogenous activators including dietary products and intermediates, thereby enabling the organism to adapt quickly to environmental changes by regulating appropriate metabolic processes. Altered signaling by metabolic receptors, triggered by these environmental factors, can affect the homeostatic pathways and therefore contribute to the pathogenesis of metabolic diseases including type 2 diabetes, obesity, hyperlipidemia, and atherosclerosis. For the same reasons, these xenobiotic receptors represent excellent targets for the therapeutic development of metabolic disorders. The following sections discuss how these xenobiotic receptors mediate events associated with lipid dysfunction and obesity-related diseases.

AhR in lipid metabolism

A hallmark of systemic TCDD toxicity involves an overall perturbation of energy homeostasis [49]. Earlier work had already connected the AhR agonist to dyslipidemia by reporting that TCDD and related halogenated aromatic hydrocarbons (HAHs) produced marked fatty liver in several species [50–52]. In agreement with the results from animal models, dioxin exposure in human populations has also been reported to be associated with increased incidence of fatty liver [53]. The accumulation of hepatic triglycerides was accompanied by an induction in liver weight and liver to body weight ratios [54]. Increased *de novo* fatty acid synthesis [55], decreased fatty acid oxidation [56], and increased half-life of liver lipid moieties [54] might account for the hepatic steatosis in AhR agonists-treated rats. However, some other studies showed decreased hepatic fatty acid synthesis in both animal models and primary human hepatocytes upon TCDD treatment, which was associated with reduced expressions of key lipogenic genes including FASN, SCD-1, and ACC-1 [57–59]. Cautions need to apply when interpreting these phenotypes because TCDD itself is toxic to the cells and animals, so the metabolic phenotypes could have been secondary to TCDD toxicity. In addition, other non-toxic AhR agonists, such as quercetin and indigo, have also been demonstrated to protect mice from NAFLD through modulating inflammation, oxidative stress, or the composition of gut microbiota [60]. Recently, we showed that mice overexpressing a constitutively activated AhR (CA-AhR) in the liver developed a spontaneous steatosis without causing a general hepatotoxicity. The steatosis in CA-AhR transgenic mice was manifested by increased fatty acid uptake and decreased VLDL-triglyceride secretion. CD36, the fatty acid translocase, was identified as a novel AhR target gene that mediated the steatotic effect [61]. In another independent study, mice fed with the AhR ligand 3-MC, an AhR agonist less toxic than TCDD, showed hepatosteatotic phenotype through a similar mechanism [62]. On the other hand, AhR whole-body deficiency and platelet-derived growth factor receptor alpha (Pdgfrα)-Cre-mediated AhR knockout in preadipocyte lineages and other cell types protected mice from diet-induced obesity and metabolic disorders through increased energy expenditure [63, 64], while the liver-specific AhR knock-out mice showed more severe hepatic lipotoxicity by transcriptional regulation of suppressor of cytokine signal 3 (Socs3) [65]. These results suggested that the effects of AhR on energy metabolism might be ligand-and tissue-specific.

Using the same CA-AhR transgenic mice, we recently showed that activation of AhR can also sensitize mice to non-alcoholic steatohepatitis (NASH), an advanced stage of NAFLD with the hallmarks of inflammation and progressive fibrosis [66]. The CA-AhR transgenic mice showed heightened sensitivity to methionine and choline deficient diet (MCD)-induced NASH through decreasing superoxide dismutase 2 (SOD2) activity and increasing mitochondrial reactive oxygen species (ROS) production in the liver. Mechanistically, the mitochondrial sirtuin deacetylase SIRT3, which can enhance the scavenging of superoxide through the activation of mitochondria SOD2, was inhibited by AhR. The AhR-responsive inhibition of SIRT3, a NAD+ dependent deacetylase, was likely due to the depletion of cellular concentration of NAD+ because of the activation of TiPARP by AhR [67]. Interestingly, the anti-oxidative role of AhR has also been reported. For example, the nuclear factor erythroid 2 related factor 2 (Nrf2), a master regulator of antioxidative responses, was directly induced by AhR activation, which in turn protected against the oxidative stress [68]. Other reported AhR inducible cytoprotective genes include the NAD(P)H:quinone oxidoreductase 1 (Nqo1), GSTs, and UGTs [69]. These results suggested that AhR might have a rather complex role in the liver's handling of oxidative stress.

In addition to NAFLD and NASH, activation of AhR has also been implicated in dyslipidemia and atherosclerosis. Lipid abnormalities have been reported in workers and community residents exposed to TCDD. A statistically significant positive relationship between high serum TCDD and plasma cholesterol and triglyceride levels was observed in subjects exposed to chloracne, and among US Vietnam veterans who had been exposed to high levels of TCDD [70–72]. A follow-up study on a group of former TCDD workers showed that exposure to TCDD caused atherosclerotic plaques and ischemic heart disease [73]. Animal studies confirmed that TCDD induced a marked dyslipidemia characterized by the induction of total cholesterol, VLDL, LDL, and triglyceride levels [74–76]. Mechanistically and of particular relevance to triglyceride metabolism, the adipose activity of LPL, which hydrolyses triglyceride and promotes its cellular uptake, was reduced in both animals and adipocyte cultures after TCDD treatment [77, 78]. As for the cause of hypercholesterolemia, TCDD caused a down-regulation of LDLR on the plasma membrane of hepatocytes, which accounted for the decreased cholesterol internalization and the resulting elevated plasma cholesterol levels [79]. Although it remains to be determined whether the effect of TCDD on

the expression of adipose LPL and liver LDLR is AhR dependent, it has been reported that the increase of liver LPL by TCDD was abolished in AhR knockout mice [75]. Moreover, AhR deletion could also protect mice from high fat diet-induced dyslipidemia and vascular dysfunction probably through improving eNOS/NO signaling [80].

AhR in glucose metabolism, insulin resistance, and diabetes

Dyslipidemia is a well-known predisposing factor for the development of type 2 diabetes. With the potential effects of AhR on dyslipidemia, it is reasonable to hypothesize that AhR can influence diabetes as well. Indeed, both animal models and human suggested an association between TCDD exposure and increased incidence of diabetes [81–83]. A study utilizing the AhR-null mice demonstrated that treatment with TCDD decreased the plasma insulin level in wild type mice, but not in AhR-null mice [84], suggesting that the insulin-lowering effect of TCDD was AhR dependent. Recent studies also uncovered the relationship between AhR ligand bioactivity and the incidence of type 2 diabetes or the parameters of insulin resistance [85, 86]. However, the mechanism involved in diabetes produced by higher doses of TCDD is still unclear. A reduction in glucose uptake has been reported in adipose tissue, liver, and pancreas [78, 87, 88], primarily through the decreased expression of glucose transporter 4 (GLUT4) [89]. Another suggested mechanism was the inhibition of hepatic phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase), which resulted in an impairment of gluconeogenesis [90]. In addition, non-diabetic veterans with high blood TCDD levels were more likely to develop insulin resistance [91], and TCDD-treated animals showed beta cell dysfunction including reduced insulin production and secretion [88, 92]. Based on the fact that loss of peroxisome proliferator-activated receptor γ (PPARγ) is diabetogenic, and the PPARγ agonist thiazolidinediones sensitizes tissues to the insulin actions, it was also suggested that the diabetogenic effects of TCDD might be through antagonizing the PPARγ functions [81]. More recently, our study identified the endocrine hormone fibroblast growth factor 21 (FGF21), as a direct transcriptional target of AhR, that mediates the metabolic benefit of AhR [93].

The AhR heterodimerization partner ARNT, also known as hypoxia-inducible factor 1b (HIF1b), is a ubiquitously expressed nuclear protein that also belongs to the bHLH/PAS family of transcription factors [94]. Recent findings showed that the expression of ARNT was reduced in both liver and beta cells of obese individuals with type 2 diabetes [95, 96], suggesting an important role of ARNT in the development of metabolic disease. Further studies demonstrated that the deficiency of ARNT activity in beta cells or liver contributed to impaired insulin secretion or dysregulation of glucose homeostasis and lipid metabolism, respectively [95, 96]. A recent study also showed that the loss of Arnt in the pancreatic beta cells protected mice from high-fat diet-induced diabetes [97]. The effects of AhR on lipid metabolism are summarized in Figure 3.

PXR in lipid metabolism

In recent years, PXR and CAR have emerged to have many pivotal endobiotic functions, including in the regulation of lipid homeostasis [98–100]. The expression of PXR was shown to have a moderate increase in the diet-induced NAFLD model, while the expression of primary PXR target gene Cyp3a11 was consistently increased 3–4 fold during the progression of NAFLD, which indicates the induction of PXR activation during the development of NAFLD [101]. A number of studies suggested PXR has a steatogenic effect. Transgenic mice overexpressing a constitutively activated PXR in the liver developed hepatomegaly and marked hepatic steatosis resulting from accumulation of triglycerides. In independent pharmacological models, treatment of human PXR (hPXR) "humanized" mice with the hPXR agonist rifampicin elicited a similar steatotic effect [98, 102]. The steatotic effect of PXR was also supported by the finding that hepatic steatosis was suppressed in mice lacking PXR after partial hepatectomy [103]. The pro-steatotic effect of PXR was also demonstrated in human hepatocytes and hepatoma cell lines by either pharmacological or genetic activation of PXR [104]. It was previously reported that treatment of mice with the PXR agonist PCN conferred resistance to lithocholic acid (LCA)-induced hepatotoxicity [105]. Recently, it was suggested that in addition to the PXR-mediated induction of the drug metabolizing enzymes, PCN-mediated stimulation of lipogenesis might have also contributed to the protection against LCA-induced liver injury [106]. Consistent with the notion that steatosis is the first step in the development of NAFLD, a case-control association study investigating 290 individuals revealed that PXR genetic variants might contribute to disease severity in NAFLD by influencing the individual susceptibility to progress to more severe stages of the disease [107]. Furthermore, post translational modifications of PXR also play roles in steatosis. A study using primary hepatocytes showed that PXR acetylation status alone can regulate lipogenesis independent of

ligand activation [108], while another recent study demonstrated that Ser347 phosphorylation of PXR might have helped to prevent the liver from fasting-induced steatosis and hypertriglyceridemia [109].

Mechanistically, the steatotic effect of PXR is likely the result of a combined effect of increased hepatic fatty acid uptake, increased lipogenesis, and suppression of fatty acid β-oxidation [98]. Activation of PXR increased fatty acid uptake through the induction of hepatic CD36, and several other accessory lipogenic enzymes, including SCD-1, long chain free fatty acid elongase, and PPARγ [98]. Promoter analysis established CD36 as a direct transcriptional target of PXR. Moreover, PPARγ2, a positive regulator of CD36, was also shown to be a direct transcriptional target of PXR [110]. These results suggested that PXR regulated CD36 gene expression directly or through crosstalk with PPARγ [35, 111]. Independent reports suggested that activation of PXR induced *de novo* lipogenesis through the direct induction of the thyroid hormone (TH)-responsive spot 14 protein (S14), which is known to transduce hormone-related and nutrient-related signals to genes involved in lipogenesis [112]. Our recent results suggested that lipin-1, the expression of which is known to increase triglyceride synthesis, was a potential PXR target, providing another possible explanation for the lipogenic effect of PXR in the liver [113]. Another study also reported the solute carrier family 13 member 5 (SLC13A5) as a PXR target gene that mediated PXR's contribution to drug-induced steatosis and metabolic disorders in humans [114]. In addition to increasing lipogenesis, the steatotic effect of PXR was also associated with suppression of several genes involved in fatty acid β-oxidation such as PPARα and thiolase [98]. CPT1a and HMGCS2, respective rate-limiting enzymes for β-oxidation and ketogenesis, were inhibited after treatment of mice with PCN, and this effect was achieved by direct binding of activated PXR to Forkhead box A2 (FoxA2), thereby preventing FoxA2 binding to its target genes including Cpt1a and Hmgcs2 [115]. A recent report suggested that gut microbiome may have mediated the steatotic effect of PXR [116].

PXR also plays a critical role in regulating lipoprotein homeostasis. Treatment of HIV patients or epileptic patients with protease inhibitors or antiepileptic drugs, both of which are potent PXR agonists, increased total and LDL cholesterol levels [117–122]. Several dietary contents such as Cafestol and sulforaphane, which could alter plasma lipid levels, were found to be PXR agonists or antagonists [123, 124]. In animal models, PXR activation led to increased levels of the atherogenic lipoproteins VLDL and LDL [99, 125]. A recent study demonstrated that PXR activation induced circulating atherogenic lipids together with the plasma proprotein convertase subtilisin/kexin type 9 (PCSK9), a negative regulator of hepatic LDL uptake, potentially through increased proteolytic activation of sterol regulatory element-binding protein 2 (SREBP2) [126]. A genome-wide association study showed that genetic variants in PXR could affect plasma LDL levels in humans [127]. Alterations of several genes involved in HDL metabolism accounted for the atherogenic effect of PXR activation, including decreased ABCA1 and ApoA-I in HDL assembly, reduced LCAT and phospholipid transfer protein (PLTP) in HDL maturation, and decreased SR-BI in clearance [125, 128]. However, in several other studies, activation of PXR has been shown to exert a beneficial effect on HDL levels, which was associated with increased ApoA-I levels [129, 130]. In addition, the effect of lovastatin on lowering cholesterol in human liver cells was found dependent on PXR activation [131]. The effects of PXR on lipid metabolism are summarized in Figure 3.

CAR in lipid metabolism

In contrast to the lipogenic effect of PXR, activation of CAR suppresses lipogenesis. Treatment with the CAR agonist TCPOBOP alleviated hepatic steatosis and inhibited the expression of lipogenic genes including Srebp-1c, Acc-1, Fas, and Scd-1 in both diet-induced and genetic obese mouse models [132, 133]. For the mechanism of the inhibitory effect of CAR on lipogenesis, Roth and colleagues reported that activation of CAR induced the expression of Insig-1, a protein with anti-lipogenic properties, and resulted in a reduction in the active SREBP-1 level [134]. Promoter analysis suggested Insig-1 as a direct CAR target gene. An independent study suggested that activation of CAR can trans-suppress the lipogenic nuclear receptor LXR by inhibiting the recruitment of LXRα to the Srebp-1c gene promoter [135]. A recent study also reported fibronectin type III domain-containing protein 5 (Fndc5)/Irisin as a direct CAR target gene that can inhibit lipogenesis and gluconeogenesis via the adenosine 5′-monophosphate (AMP)-activated protein kinase pathway [136].

CAR also regulates the metabolism of lipoproteins, but the effects of CAR activation on plasma lipoprotein levels in rodents and humans are inconclusive or ambiguous. TCPOBOP, a CAR agonist, decreased plasma HDL and apoA-I levels in WT and human apoA-I transgenic mice [137], and CAR null mice exhibited higher HDL levels under cholestatic conditions after bile duct ligation [138]. Phenobarbital, another CAR agonist, was shown to increase plasma cholesterol and lipoprotein levels [122]. In

contrast, treatment with phenytoin, a nonspecific CAR agonist, increased the HDL levels in humans [139, 140]. CAR activation was also able to stimulate the elimination of cholesterol derived from HDL via its conversion into bile acids during diet-induced hypercholesterolemia, which improves the cholesterol homeostasis [141]. The effects of CAR on lipid metabolism are summarized in Figure 3.

CAR and PXR in glucose metabolism, insulin resistance, and diabetes

In addition to impacting on lipid metabolism, CAR and PXR also play a role in glucose homeostasis and insulin resistance. Treatment with the CAR agonist TCPOBOP inhibited gluconeogenesis and alleviated insulin resistance in both the high-fat diet and ob/ob mouse models in a CAR-dependent manner [132, 133]. Our most recent study also demonstrated that CAR activation attenuated gestational diabetes mellitus-sensitized and HFD-induced obesity and type II diabetes [142]. In contrast, the CAR null mice showed spontaneous defect in insulin sensitivity [132, 133]. The anti-diabetic effect of CAR in mice was consistent with the clinical observation that chronic treatment of diabetic patients with phenobarbital decreased plasma glucose and improved insulin sensitivity [143]. The expression of the gluconeogenic enzyme genes Pepck and G6Pase was suppressed in CAR-activated mice. The detailed mechanism by which CAR inhibited gluconeogenesis remains to be clearly defined. The forkhead box protein O1 (FoxO1), peroxisome proliferative activated receptor-γ co-activator 1α (PGC-1α) and hepatocyte nuclear factor 4α (HNF4α) are three important positive regulators of gluconeogenesis in the liver [144]. Liganded CAR was reported to repress FoxO1 in its binding to the promoters of gluconeogenic enzyme genes [145, 146]. CAR can also compete with HNF4α for the DR1 binding motif, and dissociate the coactivator PGC1α from HNF4α, thereby suppressing gluconeogenesis [146, 147]. Our mechanistic study revealed an unexpected function of CAR in recruiting PGC1α to the Cullin1 E3 ligase complex for ubiquitination, which might be a cellular adaptive mechanism to accommodate energy-restricted conditions [148]. It is noted that many of these mechanistic studies are cell culture work whose *in vivo* relevance remains to be validated. Our recent *in vivo* study showed that the CAR coactivator, growth arrest and DNA damage-inducible gene 45b (Gadd45b), is in part required for the anti-obesity effects of CAR activation [149]. The inhibition of hepatic lipogenesis, gluconeogenesis and adipose inflammation by TCPOBOP treatment was abolished in Gadd45b knockout mice.

The effect of PXR on glucose metabolism and insulin resistance is more controversial. We previously reported that PXR ablation alleviated high fat diet-induced insulin resistance. In an independent model, introducing the $PXR^{-/-}$ allele into the ob/ob background also relieved the diabetic phenotype. The ob/ob mice deficient of PXR showed inhibition of gluconeogenesis and an increased rate of glucose disposal during euglycemic clamp. In contrast, transgenic activation of PXR worsened the diabetic phenotype [113]. The detrimental effect of PXR activation was supported by an independent report that administration of PXR agonists PCN and rifampin impaired postprandial glucose tolerance during the oral glucose tolerance test (OGTT) in rats and healthy human subjects, which might be due to a down-regulation of hepatic GLUT2, the major hepatic glucose transporter facilitating the glucose influx at high plasma glucose [150]. Recent mechanistic studies also demonstrated that PXR activation could downregulate GLUT2 expression as well as internalize GLUT2 protein from the plasma membrane to the cytosol, and impair glucose uptake and utilization in the liver [151, 152]. Based on these results, it was concluded that the metabolic effect of PXR *in vivo* was opposite of that reported for CAR [113]. It was noted that treatment of WT mice with PCN has been reported to inhibit G6Pase and Pepck gene expression [145, 153], but those observations were made in chow diet fed mice after a brief PXR ligand treatment. The discrepancies may have resulted from different nutritional and/or metabolic status, a notion that is also supported by our observation that the suppression of G6Pase and Pepck seen in chow-fed VP-PXR transgenic mice [98] was absent in ob/ob mice that carry the same transgene [113]. The role of PXR in glucose metabolism may also have species specificity. In the human hepatocytes, statin-activated PXR upregulates gluconeogenic genes G6Pase and PEPCK by stimulating protein phosphatase 2C (PP2C) to dephosphorylate serum/glucocorticoid regulated kinase 2 (SGK2) which then co-activates PXR-mediated transcription, while this pathway is not present in the mouse liver [154].

Summary and future directions

Starting from late 1990s, significant advances have been achieved in our understanding of the typical functions of xenobiotic receptors as master regulators of xenobiotic metabolism and disposition. In more recent years, emerging evidence has shown that xenobiotic receptors, such as AhR, PXR, and CAR, can also play major roles in lipid and glucose metabolism, by which they can influence

the pathogenesis of related diseases, including dyslipidemia, NAFLD, NASH, obesity and type II diabetes, and atherosclerosis. Thus, despite their potential adverse effects of drug-drug interactions, therapeutics that target the "xenobiotic receptors" can potentially be beneficial in managing metabolic disease by impacting lipid and glucose metabolism.

Future studies are necessary to better understand the molecular mechanisms by which xenobiotic receptors regulate lipid and glucose metabolism. There were also reports of inconsistent effects of xenobiotic receptors in patients and animal models, so future use of humanized mice as well as more human studies are necessary to further clarify the human relevance of the role of xenobiotic receptors in lipid metabolism and metabolic disease. Moreover, many of the published studies realized the manipulation of xenobiotic receptors at the systemic level by using whole-body knockout mice or systemic ligand administration, which prevented the conclusions of tissue-specific roles of these receptors. Future studies that utilize conditional activation or knockout models may help with the mechanistic understanding at the resolutions of organs or cell types with an organ.

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