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Review

Deciphering the roles of the constitutive androstane receptor in energy metabolism

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The constitutive androstane receptor (CAR) is initially defined as a xenobiotic nuclear receptor that protects the liver from injury. Detoxification of damaging chemicals is achieved by CAR-mediated induction of drug-metabolizing enzymes and transporters. More recent research has implicated CAR in energy metabolism, suggesting a therapeutic potential for CAR in metabolic diseases, such as type 2 diabetes and obesity. A better understanding of the mechanisms by which CAR regulates energy metabolism will allow us to take advantage of its effectiveness while avoiding its side effects. This review summarizes the current progress on the regulation of CAR nuclear translocation, upstream modulators of CAR activity, and the crosstalk between CAR and other transcriptional factors, with the aim of elucidating how CAR regulates glucose and lipid metabolism.

Keywords: nuclear receptor; constitutive androstane receptor; xenobiotic metabolism; metabolic diseases; energy metabolism

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Introduction

CAR (NR3I1) belongs to the nuclear receptor superfamily that exhibits enriched expression in the small intestine, liver, and gallbladder[1]. CAR was initially defined as a xenobiotic nuclear receptor that mediates the hepatic detoxification of foreign chemicals and endogenous bile acids[2]. Together with other xenobiotic nuclear receptors, such as the pregnane X receptor (PXR), CAR senses xenobiotic stimuli and elicits their clearance by transactivating cytochrome P450 (CYP) enzymes and phase 2 conjugating enzymes, as well as drug transporters (*eg*, CYP2Bs, MRPs, and UGTs)[3, 4]. On the promoters of these target genes, CAR directly binds to the proximal xenobiotic responsive element (XRE) and/or the distal phenobarbital responsive enhancer module (PBREM), where it heterodimerizes with the retinoid X receptor (RXR)[5, 6]. Up-regulation of these target genes leads to the elimination of toxic chemicals and drug metabolites and prevents hepatotoxicity. Meanwhile, CAR-induced drug-metabolizing enzymes and transporters are also responsible for the removal of hydrophobic bile acids from the liver. Detoxification of bile acids to less damaging metabolites and the export of bile acids protect hepatocytes from cholestasis[7–10].

Microarray analysis has suggested that CAR not only induces drug-metabolizing genes but also influences the expression of genes involved in glucose/lipid metabolism as well as those responsible for hepatocyte proliferation[11–13]. Follow-up pharmacological and biochemical studies have expanded our understanding of the pathophysiological function of CAR beyond xenobiotic metabolism. Activation of CAR improves glucose and lipid metabolism in metabolic diseases, which highlights it as a promising therapeutic target for metabolic syndromes[14]. However, obstacles exist for the clinical use of CAR activators due to the concerns of drug-drug interaction, hepatomegaly and liver carcinogenesis[15]. A better understanding of the mechanism by which CAR modulates energy metabolism will help in overcoming these obstacles. This review is dedicated to the molecular basis of the regulation of CAR activity and CAR's crosstalk with other proteins. We will also discuss how we may be able to better harness the metabolic benefits of CAR by better understanding its mechanistic properties.

Nuclear translocation of CAR

The response of CAR to xenobiotic exposure is very fast. For example, *Cyp2b10* gene expression peaks within one hour upon acute treatment with 1,4-bis-[2-(3,5-dichloropyridyloxy)]

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benzene,3,3′,5,5′-tetrachloro-1,4-bis(pyridyloxy)benzene (TCPOBOP) in mice[12]. Such a rapid response is achieved primarily by massive nuclear translocation of CAR from the cytoplasm[16]. Therefore, substantial efforts have been devoted to delineate the mechanism of the cytoplasmic retention and nuclear translocation of CAR (Figure 1). In the past decade, Masa NEGISHI's group and others have identified several key proteins that participate in the phenobarbital-induced nuclear translocation of CAR. Phosphorylation and de-phosphorylation play an important role in regulating the nuclear translocation of CAR. Human CAR residue threonine 38 (corresponding to mouse CAR residue threonine 48) is a conserved protein kinase C (PKC) target site. A mutation study showed that T38A, which is unable to be phosphorylated, mimics the effect of phenobarbital treatment. In contrast, T38D, which resembles phosphorylated CAR, is largely retained in the cytoplasm[17]. These results suggested that phosphorylation at threonine 38 is a repressive signal for the nuclear translocation of CAR. However, further studies are needed to elucidate the upstream pathways of PKC. Hepatic growth factors negatively regulate the phenobarbital-mediated induction of *CYP2B* through activation of signaling cascades, including mitogen-activated protein kinase kinase (MEK) and extracellular signal-regulated kinase (ERK). Moreover, active ERK sequesters phosphorylated CAR in the cytoplasm[18]. Alternatively, okadaic acid, a protein phosphatase 2A (PP2A) inhibitor, diminishes the phenobarbital-mediated induction of *CYP2B* expression in primary rat hepatocytes, suggesting that PP2A is the phosphatase for CAR and is involved in the activation of CAR[19]. In a more recent study, the PP2A core enzyme was found to be recruited to phosphorylated CAR by the receptor for activated C kinase 1 (RACK1) and to de-phosphorylate CAR[20]. RACK1 seems to preferentially bind to phosphorylated threonine 38. However, de-phosphorylation of CAR is not limited to threonine 38, considering that the de-phosphorylation of serine 202 is also required for CAR nuclear translocation[21]. RACK1 is negatively regulated by Src kinase, which functions downstream of the epidermal growth factor receptor (EGFR) pathway. Phosphorylation of RACK1 by Src prevents its interaction with CAR. Phenobarbital, demonstrated as a potential antagonist of EGFR, competes with EGF binding to EGFR, therefore abrogating the blockade of RACK1 by activating the EGFR cascade[20]. Taken together, the two signaling branches downstream of EGFR, MEK-ERK, and Src-RACK1, integrate at cytoplasmic CAR to inhibit its nuclear translocation. Note that one of the protein phosphatase 1 cata-

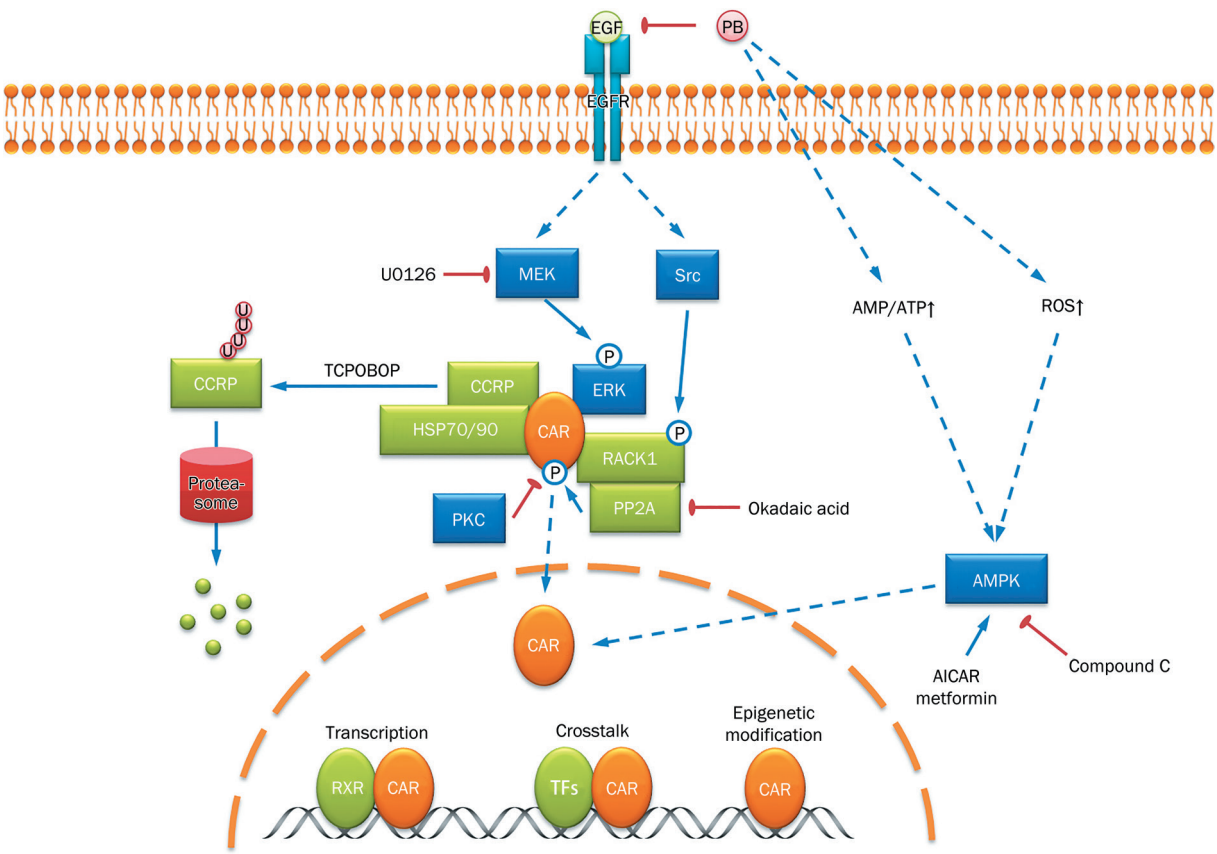

Figure 1. Regulation of CAR nuclear translocation and activity. CAR cytoplasmic retention is regulated by upstream phosphorylation cascades and cytoplasmic chaperones. Phenobarbital antagonizes EGFR and de-suppresses CAR, and TCPOBOP triggers ubiquitination and proteasomal degradation of CCRP. Nuclear CAR is also regulated by AMPK and ROS and elicits its effect through transcriptional activity, crosstalk with other transcriptional factors, and epigenetic modifications.

lytic subunits, PPP1R16A, interacts with CAR at the cell membrane and prevents nuclear translocation of CAR, which is dependent on phosphatase activity[22]. Moreover, the mitogen-activated protein kinase (MAPK) p38 also regulates human CAR activity on the *CYP2B6* gene[23]. This additional evidence adds further complexity to the phosphorylation-dependent nuclear translocation of CAR.

In addition to phosphorylation and de-phosphorylation, several other proteins are also involved in the cytoplasmic retention of CAR. Heat shock protein 90 (HSP90), a chaperone protein that serves as a cellular stress sensor, is associated with the glucocorticoid receptor (GR) and aryl hydrocarbon receptor (AhR). Together with immunophilin or immunophilin-like protein, HSP90 governs the nuclear translocation of GR and AhR in a ligand-dependent manner. Similarly, CAR is also associated with HSP90[24]. Cytoplasmic CAR retention protein (CCRP) forms a ternary complex with HSP90 and CAR and retains CAR in the cytoplasm[25]. Intriguingly, several facts strongly imply that cytoplasmic retention by the CCRP-HSP90 complex is an adaptive mechanism that leads to the accumulation of CAR in the cytoplasm to quickly respond to a second exposure of stress. First, the HSP90-CAR complex recruits PP2A in the presence of phenobarbital, indicating that the ternary complex is necessary for CAR de-phosphorylation, which is a critical event for CAR nuclear translocation[24]. Second, the CAR-HSP90-CCRP ternary complex is associated with the cellular skeleton, and inhibition of HSP90 or disruption of the microtubule network disturbs the nuclear translocation of CAR, further demonstrating that the complex is essential for the nuclear translocation of CAR[26]. Third, the accumulation of CAR in the cytoplasm is not derived from nuclear exclusion because CCRP does not affect the nuclear content of CAR[25]. A recent study has explained how the components of the ternary complex are coordinated[27]. Upon cellular stresses (*eg*, thermal stress), CAR is enriched in the CAR-HSP70/90-CCRP ternary complex. Upon treatment of TCPOBOP, CCRP undergoes ubiquitination and proteasomal degradation, which facilitates the nuclear translocation of CAR.

Although the molecular mechanism for the nucleocytoplasmic translocation of CAR has been established based on the studies discussed above, questions still remain for the regulation of CAR nuclear translocation. AMP-activated protein kinase (AMPK) has been long known to mediate phenobarbital-induced CAR activation[28–30]. However, the results from the mechanistic study of the AMPK-dependent activation of CAR leave much to be desired. Phenobarbital seems to increase the AMP/ATP ratio and promote liver kinase B1 (LKB1)-mediated AMPK activation[31]. Another pathway involving the microRNA miR-122 is also associated with AMPK activation[32]. Because of the lack of evidence on AMPK downstream targets, it remains unclear how AMPK activation influences CAR nuclear translocation. Pharmacological activation of AMPK seems to down-regulate HSP70 and EGFR and activate PP2A, suggesting that AMPK may trigger CAR nuclear translocation through the regulation of suppressive proteins[33–35]. In addition, how some of the coactivators drive ligand-independent nuclear translocation of CAR *in vivo* is still unclear. Steroid receptor coactivator 2 (SRC2/GRIP1) induces the phenobarbital-independent nuclear translocation of CAR[36]. Peroxisome proliferator-activated receptor (PPAR)-binding protein (PBP/MED1), one of the components of the mediator complex, is also required for the nuclear translocation of CAR *in vivo*[37]. Whether those coactivators trigger CAR nuclear translocation by disruption of the retention complex or independently through other mechanisms remains to be understood.

Transcriptional regulation of CAR

Whereas immediate early responses leading to the nuclear translocation and activation of CAR quickly defend the intracellular environment against external xenobiotic insults, long-term protection through CAR can be augmented by transcriptional up-regulation of the *CAR* gene itself. Many chemicals from drugs and herbal medicines as well as environmental exposure have been shown to increase the expression of CAR[38]. Under those circumstances, AhR is likely an upstream transcriptional factor that positively regulates *CAR*[39]. Glucocorticoids (*eg*, dexamethasone) efficiently induce CAR expression in human primary hepatocytes at a nanomolar dose[40]. A distal glucocorticoid response element (GRE) was found on the *CAR* gene promoter, suggesting that CAR is a direct target gene of GR. Thyroid hormones, through activation of the thyroid receptor (TR), are able to induce CAR expression at physiological concentrations[41]. Alternatively, activated CAR affects serum thyroid hormone concentrations and influences thyroid-follicular cell proliferation[42]. All-*trans* retinoic acid, a metabolite of vitamin A, was also found to up-regulate CAR mRNA through the retinoic acid receptor (RAR)[43]. Endogenous hormones and endobiotic metabolites appear to be very important for the maintenance of basal CAR expression.

Several studies have also shown that CAR expression is highly inducible during the feeding-fasting switch. Fasting-dependent induction of CAR is mediated primarily by hepatocyte nuclear factor 4α (HNF4α) and PPARα[44, 45]. Whereas fasted WT mice exhibit a higher CAR mRNA level compared with fed mice, this fasting response is almost completely attenuated in either HNF4α or PPARα knockout mice. HNF4α and PPARα responsive elements were found on the promoter of CAR, indicating that HNF4α and PPARα directly bind to the promoter of CAR and induce CAR expression. Moreover, PPARγ coactivator 1α (PGC1α) coactivates HNF4α and PPARα on the CAR promoter and coactivates CAR on the *Cyp2b10* promoter and possibly others, which may contribute to the amplification of CAR downstream genes[45]. In addition, the expression of CAR and some of its downstream target genes fluctuates in accordance with the diurnal rhythm, indicating that the circadian rhythm also has an impact on the expression of CAR[46, 47]. RAR-related orphan receptors (RORs) and Rev-erbs are master regulators for the circadian rhythm[48]. Whether the circadian expression of CAR is mediated by RORs and/or Rev-erbs would be interesting to determine. Last but not least, miR-137 negatively regulates *CAR* mRNA,

suggesting that microRNA-mediated gene silencing is another mechanism governing CAR expression[49].

Modulators of CAR activity

As a typical nuclear receptor, CAR is composed of the N-terminal AF1 ligand-independent domain, DNA-binding domain (DBD), and ligand-binding domain (LBD). Crystal structure analysis revealed that the LBD amino acids on CAR form a pocket that is responsible for the high binding affinity for the Leu-X-X-Leu-Leu (LXXLL) motif, a conserved motif found in many nuclear receptor coactivators[50]. A number of coactivators have been found to physically interact with CAR[51]. The three members of p160 coactivators, SRC1, SRC2, and SRC3, as well as PGC1α have been reported to enhance the activity of CAR based on reporter gene assays[52–57]. The function of individual coactivators seems to be redundant, at least for the induction of mouse *Cyp2b10*[58]. However, an *in vivo* deficiency of SRC3 impaired TCPOBOP-induced hepatic hyperplasia and drug-metabolizing enzymes, indicating that the coactivation of CAR by different coactivators can be involved in different genomic contexts[59]. Loss-of-function studies have identified more coactivators that are essential for the full activity of CAR. For example, a dominant negative fragment of activating signal cointegrator (ASC2/NcoA6) abolished TCPOBOP-induced gene expression and prevented acetaminophen-induced liver toxicity[60]. In PBP knockout mice, the nuclear translocation of CAR is blocked in the presence of phenobarbital[37]. Loss of the protein growth arrest and DNA-damage-inducible β (GADD45β) in hepatocytes attenuated *Cyp2b10* induction by TCPOBOP[61]. The LXXLL-binding pocket can also be targeted by some corepressors. Like many other nuclear receptors, CAR is also bound and repressed by the following common corepressors: nuclear receptor corepressor 1 (NCoR1), NCoR2/SMRT, and DAX-1 (NR0B1)[53, 54, 57, 62]. Collectively, the LXXLL-mediated direct interaction of CAR and its cofactors is very important for the activity of CAR. More importantly, because CAR shares multiple coregulators with other transcriptional factors, coregulator exchange and competition may influence many cellular processes when CAR is activated[63].

CAR has also been shown to functionally crosstalk with many transcriptional factors. The outcome of crosstalk is either stimulatory or inhibitory. The transcriptional factors that potentiate the activity of CAR include HNF4α, CCAAT-enhancer-binding protein α (C/EBPα), activating transcription factor 5 (ATF5), nuclear factor (erythroid-derived 2)-like 2 (Nrf2), and hypoxia-inducible factor 1 (Hif1)[64–67]. Much of the crosstalk occurs between specific genes. Whether such crosstalk could be extended to the regulation of other genes needs to be further tested. CAR inducible genes are overlapped with AhR, PXR, PPARα, and Nrf2, indicating that CAR's crosstalk with these transcriptional factors will contribute to the coordinated regulation of xenobiotic detoxification, fasting responses, and anti-oxidant responses[68]. Overlapping gene induction could be due to different cis-acting elements on specific target genes, which may result in some additive effects. Nevertheless, with the help of additional factors, crosstalk between CAR and other transcriptional factors will be facilitated and will exhibit synergistic effects[67, 69–71]. However, several CAR inhibitory factors, such as sterol regulatory element-binding protein 1 (SREBP1), liver X receptor (LXR), farnesoid X receptor (FXR), estrogen receptor (ER), and histone deacetylase 1 (HDAC1), also exist[72–76]. The inhibitory crosstalk attenuates CAR activity and down-regulates drug-metabolizing enzymes. Conversely, CAR-mediated suppression of certain transcriptional factors, such as HNF4α and LXR, leads to inhibition of glucose and lipid metabolism. In general, the mutual inhibitory effects are due primarily to competitive binding to the conserved elements on the DNA and/or the coactivators that are shared. As further discussed, the crosstalk between CAR and nuclear transcriptional factors may provide links between xenobiotic metabolism and energy metabolism.

CAR in energy metabolism

CAR has been long implicated in xenobiotic metabolism. The role of CAR in energy metabolism did not receive much attention until several studies within the past few years demonstrating that CAR activation influences glucose and lipid metabolism (Figure 2). Hyperglycemia and dyslipidemia are the hallmarks of obesity-associated type 2 diabetes. Activation of CAR by the synthetic agonist TCPOBOP increased insulin sensitivity and ameliorated liver steatosis in both high fat diet (HFD)- and leptin deficiency-induced obesity[77, 78]. Several studies have shown that pharmacological activation and the genetic gain-of-function of CAR leads to lower hepatic triglyceride levels, whereas loss of CAR causes basal accumulation of triglycerides in the liver[79]. The LXR-SREBP pathway plays a central role in hepatic lipogenesis by transducing the genes involved in fatty acid biosynthesis and lipid uptake[80]. Crosstalk between CAR and LXR causes mutual repression through coactivator-binding competition. Consequently, the expression of LXR target genes are down-regulated, including lipogenic genes, such as *Srebp1*, *Acc1*, *Fas*, and *Scd1*[75]. CAR also directly binds to SREBP1, which suggests potential crosstalk between CAR and SREBP1 in the context of lipogenesis, although further functional and mechanistic studies are needed to prove this association[76].

CAR can also influence lipid biosynthesis through downstream target genes. Insulin-induced gene-1 (Insig-1) is an endoplasmic reticulum-bound cholesterol sensor that suppresses the proteolytic activation of SREBPs when sterols are abundant[81]. CAR binds to the DR4 element on the Insig-1 promoter and directly induces the expression of Insig-1, therefore preventing SREBP1 from entering the nucleus to induce lipogenic genes[79]. Unlike Insig-1 that directly targets the activation of SREBP1, sulfotransferase 2B1b (Sult2B1b), another CAR responsive gene, inhibits Srebp1 expression and hepatic lipogenesis through enzymatic deactivation of LXR ligands. Sult2B1b belongs to the subfamily of cytosolic sulfotransferases, mediating the sulfonation of oxysterols such as 22-hydroxycholesterol, 24S-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, and 24,

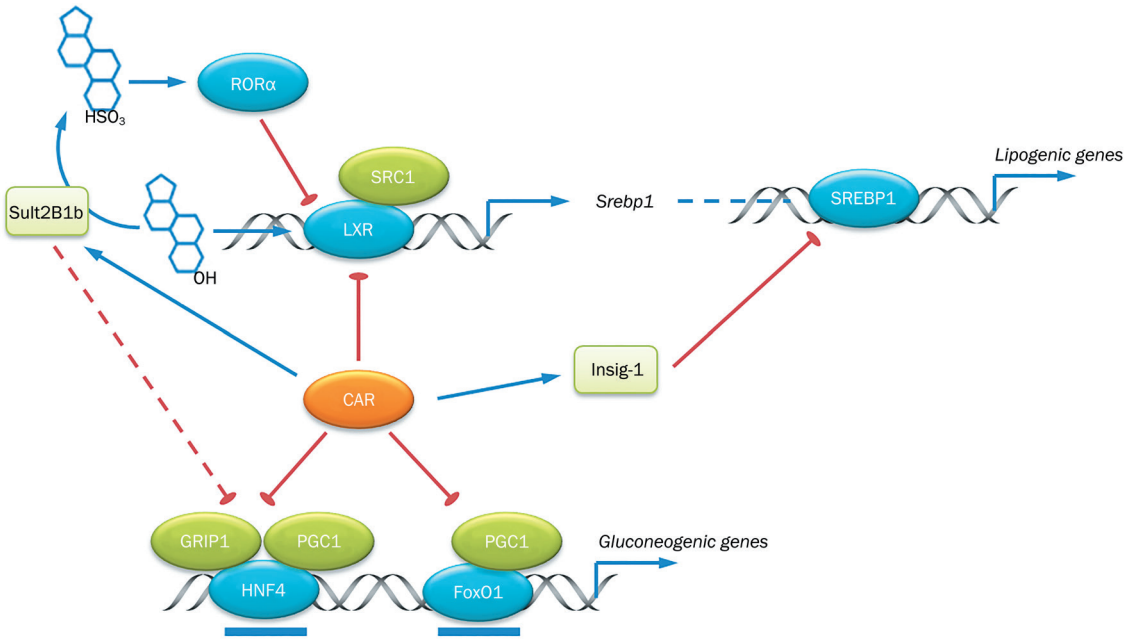

Figure 2. Inhibitory effect of CAR on glucose and lipid metabolism. CAR regulates gluconeogenic and lipogenic genes through competitive binding to *cis*-acting elements, coactivator quenching, and/or induction of suppressive genes (Sult2B1b and Insig-1).

25-epoxycholesterol[82]. Those endogenous oxysterols are potent ligands for LXR activation. Sulfonation of oxysterols reduces their capacity to activate LXR and down-regulates the LXR-SREBP pathway[83]. Consistently, the TCPOBOP-induced reduction of lipogenic genes is abolished in Sult2B1b knockout mice[78]. Liver-specific overexpression of Sult2B1b, either by adenoviral delivery or transgenic strategy, ameliorates dyslipidemia in a diabetic mouse model[84, 85]. In addition to deactivating LXR ligands, the products of sulfonation, such as 25-hydroxycholesterol-3-sulfate, have been reported to decrease lipid accumulation and inflammation[86–89]. Cholesterol sulfates, which are converted from cholesterol by Sult2B1b, have also been reported to be potent agonists for RORα[90]. Inhibitory crosstalk between RORα and LXR could be another reason for the down-regulation of lipid accumulation when Sult2B1b is overexpressed[91].

Activation of CAR not only tightly regulates lipid metabolism but also impacts hepatic glucose metabolism. Diabetic mice displayed better glucose tolerance when treated with TCPOBOP[78]. Improved glucose tolerance is due primarily to the suppression of hepatic gluconeogenesis rather than glucose disposal in white adipose tissue and skeletal muscle, as shown by a hyperinsulinemic-euglycemic clamp study in *ob/ob* mice. In agreement with lower hepatic glucose production, the two rate-limiting gluconeogenic enzymes *Pepck* and *G6pase* were down-regulated by CAR activation. Several models were proposed to explain the inhibition of gluconeogenesis by CAR. In the first model, CAR competes with forkhead box protein O1 (FoxO1) and HNF4α on the insulin responsive sequence (IRS) and DR1 element, respectively, on the promoters of *Pepck* and *G6pase*[92]. In the second model, CAR competitively binds to SRC2/GRIP1 and PGC1α, which are two coactivators of HNF4α, thus diminishing the expression of gluconeogenic genes[93]. HNF4α-mediated gluconeogenic transactivation is also controlled by nuclear HNF4α exclusion. Acetylation of HNF4α is an essential event for HNF4α translocation into the nucleus. Indeed, cholesterol sulfate and Sult2B1b were recently reported to inhibit gluconeogenesis through the deacetylation of HNF4α[85]. Therefore, up-regulation of Sult2B1b by CAR may have also played a role in the suppression of gluconeogenesis.

Insulin resistance is associated with elevated plasma lipoproteins, very-low-density lipoprotein (VLDL) production, and plasma low-density lipoprotein (LDL)[94, 95]. Subsequent atherosclerotic lesions are a serious cause for the cardiovascular complications that arise in patients with type 2 diabetes. CAR activation has been shown to decrease VLDL secretion and plasma cholesterol concentration in apolipoprotein A-I (apoA-I) transgenic mice and *Ldlr–/–* mice, partially through the down-regulation of apoA-I and up-regulation of *Vldlr*, respectively[96, 97]. Excessive cholesterol levels in the liver are also eliminated in the form of bile salts into the feces[98]. In this process, the genes responsible for the conversion of cholesterol to bile salts and bile acid hydration, conjugation, and export are up-regulated in response to TCPOBOP in the liver. In the intestine, bile acid excretion is further facilitated by the inhibition of bile acid reabsorption machinery, most likely through the inhibition of LXR. In addition, VLDL secretion and lipid homeostasis are also maintained by HNF4α[99]. The inhibitory effect of CAR on HNF4α may explain its benefits on cholesterol metabolism. Overall, CAR activation attenuates the development of atherosclerotic lesions and has a therapeutic

potential for prevention of diabetes-associated cardiovascular diseases.

Despite the fact that CAR activation lowers plasma cholesterol levels, the genes involved in *de novo* cholesterol biosynthesis are up-regulated by CAR activation[100]. Considering that hepatic cholesterols are prone to be metabolized into bile acids, the up-regulation of cholesterol biosynthesis could be a compensatory mechanism to maintain intracellular cholesterol homeostasis[101]. Interestingly, although *de novo* cholesterol and triglyceride biosynthesis share the same transcriptional factors such as SREBP, cholesterol biosynthesis seems to be selectively elevated. One explanation is that lipogenic genes are also directly regulated by other nuclear transcription factors, such as LXR and carbohydrate-responsive element-binding protein (ChREBP), but whether crosstalk between CAR and those transcription factors are necessary for the inhibitory effect on triglyceride accumulation needs to be further investigated[102, 103]. In addition, preferential *de novo* cholesterol biosynthesis can be achieved by selective activation of SREBP2[104]. Whether CAR interplays with SREBP2 to activate cholesterol biosynthesis remains to be determined.

Conclusions and perspectives

CAR is regulated not only by environmental cues, such as xenobiotic exposure and circadian rhythm, but also by endogenous metabolic signaling. High basal activity, rapid drug response, and versatile gene induction make CAR an intriguing therapeutic target. Recent research has revealed that CAR, the formerly known xenobiotic nuclear receptor, exhibits previously unknown functions in energy metabolism. Most of the metabolic benefits of CAR are observed in metabolic disease models, such as diet-induced obesity, suggesting that CAR inhibits certain factors that are highly inducible in metabolic disorders. Indeed, through the crosstalk with transcriptional factors involved in gluconeogenesis and lipogenesis, activation of CAR ameliorates hyperglycemia and dyslipidemia associated with metabolic diseases and increases systemic insulin sensitivity. The modes of action for such inhibitory effects may include the following: (1) competitive binding to *cis*-acting elements; (2) coactivator quenching; and (3) induction of suppressive genes, leading to direct inhibition of certain transcriptional factors, deactivation of pro-diabetic agonists or production of anti-diabetic substances, and changes in metabolite profiles. In addition, the metabolic benefits can also be transmitted to offspring due to permanent epigenetic switches[105, 106]. In summary, CAR is a potential therapeutic target for the prevention and treatment of metabolic diseases. However, the potential to stimulate carcinogenesis presents an obstacle for clinical use. Moving forward, mechanistic studies that dissociate the beneficial effects with the unwanted side effects will be interesting. Future work for the discovery of activators that are selective for the metabolic benefits will also be important. Accumulating evidence shows that CAR is necessary for normal function in tissues in which the expression of CAR is relatively low. The human CAR agonist CITCO induces the expression of drug transporters at the blood-brain barrier, indicating that the expression of CAR in endothelial cells is important for drug resistance[107–109]. The association of CAR single-nucleotide polymorphisms with bone mineral density was also reported, and loss of CAR increased bone mass, suggesting that CAR is essential for osteoblast/osteoclast homeostasis[110, 111].

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