Minireview

The emerging roles of fatty acid translocase/CD36 and the aryl hydrocarbon receptor in fatty liver disease

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Abstract

The fatty acid translocase (FAT)/CD36 belongs to the class B scavenger receptor family. In addition to the known functions of CD36 in the uptake of oxidized low-density lipoprotein by macrophages and uptake of fatty acids by adipose tissues, skeletal muscle and heart, emerging evidence has pointed to an equally important function of CD36 in the uptake of fatty acids in the liver and the pathogenesis of fatty liver disease. Recent reports have also suggested CD36 as a shared transcriptional target of several ligand-sensing and lipogenic transcriptional factors, such as the aryl hydrocarbon receptor, and several nuclear hormone receptors, such as pregnane X receptor, liver X receptor and peroxisome proliferator activated receptor γ. Non-alcoholic fatty liver disease is common and medically significant, because it is closely related to metabolic syndrome and has a potential to progress into the more harmful non-alcoholic steatohepatitis. It is hoped that CD36 and their transcriptional regulators can represent novel therapeutic targets for the prevention and management of fatty liver disease.

Keywords: aryl hydrocarbon receptor, nuclear receptor, CD36, gene regulation, steatosis

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Introduction

Non-alcoholic fatty liver disease (NAFLD) includes a disease spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis and hepatocellular carcinoma.[1–3] NAFLD begins as the accumulation of excessive triglycerides in the liver (hepatic steatosis). If unmanaged, simple steatosis may progress into NASH, in which triglyceride accumulation is associated with inflammation. Triglyceride buildup in patients with NASH may eventually lead to the development of cirrhosis, which causes scarring of the liver. NAFLD is often associated with obesity and insulin resistance, which affects hepatic triglyceride homeostasis.[3] Hepatic steatosis can result from: (1) increased free fatty acid (FFA) supply to the liver due to increased lipolysis from visceral and subcutaneous adipose tissues and/or increased intake of dietary fat; (2) decreased FFA oxidation; (3) increased *de novo* hepatic lipogenesis; or (4) decreased hepatic very low-density lipoprotein (VLDL)-triglyceride secretion.[1] Recent studies have suggested the significance of fatty acid transporters in the development of fatty liver disease, consistent with the clinical observation that more than 60% of accumulated fatty acids in the liver are derived from the circulation in NAFLD patients.[4,5] Fatty acid uptake can be facilitated by fatty acid translocase (FAT; also known as CD36), liver fatty acid-binding protein (L-FABP) and fatty acid transport proteins (FATPs).[6,7] This article is focused on recent findings on the regulation of CD36 gene expression and the implication of this regulation in fatty liver disease.

CD36 in fatty liver disease

An overview of CD36

Hepatic uptake of fatty acids is facilitated by cell surface receptors, including CD36/FAT. CD36 belongs to the class B scavenger receptor family and is expressed on the surface of a number of cell types, including monocytes/macrophages, endothelium and smooth muscle cells.[8–14] Overexpression of CD36 confers tissues with increased fatty acid and lipoprotein influx and/or utilization. CD36 is one of the major macrophage receptors responsible for the binding and uptake of a modified, pro-atherogenic form of low-density lipoprotein (LDL), oxidized LDL. For this reason, CD36 is believed to play a critical role in the development of lipid-laden macrophage foam cells, and

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atherosclerosis. Consistent with the role of CD36 in promoting atherosclerosis, the absence of CD36 in the ApoE knockout mouse model of atherosclerosis resulted in a significantly reduced lesion area in the aortic tree after 12 weeks of Western diet feeding.[15] In addition to facilitating oxidized LDL uptake in macrophages, CD36 affects fatty acid uptake by tissues that are involved in storage or utilization, and particularly those sensitive to insulin, including adipose, skeletal muscle and heart.[16] The importance of CD36-mediated fatty acid uptake is manifested as hypoglycemia in fasted CD36 knockout mice due to a cardiac inability to uptake fatty acids and a switch to glucose as an energy substrate.[17–19]

CD36 in fatty liver disease

In addition to its role in macrophages and atherosclerosis, emerging evidence points to an important function of CD36 in controlling hepatic fatty acid uptake and a link to the pathogenesis of fatty liver disease. The basal expression of CD36 in hepatocytes is low, but is increased significantly by a high-fat diet or by the activation of nuclear receptors.[20–24] CD36 is also expressed in Kupffer cells and hepatic stellate cells.[9,25–27] Elevated levels of CD36 expression have also been observed in the ob/ob mouse model of obesity and type II diabetes.[28] Recent findings suggest that increased hepatic CD36 expression may contribute to the development of fatty liver disease under pathological conditions, such as obesity and diabetes, and as a result of eating diets high in fat.[20,29] In patients with type II diabetes, food intake triggers liver fatty acid uptake,[30] suggesting the existence of a regulatory mechanism for hepatic fatty acid transporters. In a mouse model of human familial hypercholesterolemia (low-density lipoprotein receptor [LDLR] knockout mice engineered to only express apoB100), treatment with conjugated linoleic acids, which had previously been shown to induce hepatic steatosis in a manner at least partially dependent upon the LDLR, upregulated the expression of CD36 mRNA and induced hepatic steatosis. These results suggest that CD36 could substitute for the LDLR in lipid uptake and development of steatosis.[31] Koonen *et al.*[20] reported that mice fed with a high-fat diet had a 2.6-fold increase in hepatic CD36 protein expression, paralleled by a 1.7-fold induction of hepatic triglyceride storage. Moreover, a forced expression of CD36 by adenovirus-mediated infection was sufficient to increase hepatic fatty acid uptake and triglyceride storage.[20] In the clinic, hepatic CD36 gene expression was positively correlated with liver fat content in patients with NAFLD.[32]

CD36 regulation by nuclear receptors and the implication of this regulation in fatty liver disease

CD36 has been shown to be transcriptionally regulated by several nuclear receptors, including pregnane X receptor (PXR), peroxisome proliferator-activated receptor (PPAR) γ and liver X receptor (LXR). PXR was initially identified as a xenobiotic receptor that regulates the expression of the cytochrome P450 enzymes. Subsequent studies have established PXR as a master xenobiotic receptor that plays a central role in the transcriptional control of the mammalian xenobiotic response by regulating the expression of drug-metabolizing enzymes and drug transporters.[33–37] Zhou *et al.*[24] showed that PXR has a direct role in promoting hepatic steatosis. Liver-specific transgenic mice (Alb-VP-hPXR) that express the activated human (h) PXR in the liver exhibited hepatomegaly, histological lipid accumulation and marked hepatic triglyceride accumulation. Pharmacological activation of PXR with rifampicin for five weeks in hPXR 'humanized' mice also induced significant liver triglyceride accumulation, suggesting that sustained activation of PXR is sufficient to promote steatosis. The steatotic effect of PXR was independent of sterol regulatory element-binding protein (SREBP)-1c, a master regulator of *de novo* lipogenesis. Instead, activation of PXR induced the expression of CD36 and two lipogenic enzymes, fatty acid elongase and steroyl coA desaturase (SCD)-1. Activation of CD36 gene expression was observed in both Alb-VP-PXR transgenic mice and rifampicin-treated humanized mice. Further evidence for the direct involvement of PXR in regulating CD36 included the identification of a direct repeat (DR)-3-type PXR response element in the promoter region of the CD36 gene. Interestingly and for reasons to be determined, the regulation of CD36 by PXR is liver-specific.[24]

In addition to the direct regulation of CD36 by PXR, PXR may regulate the expression of CD36 by transactivating PPARγ, another positive regulator of CD36.[38] By using liver-specific (Alb-VP-PXR) or liver- and intestine-specific (FABP-VP-PXR) transgenic mice, Zhou *et al.*[23] showed selective induction of PPARγ by PXR in the liver, but not in the intestine. In the same study, the authors showed that the mouse PPARγ2 gene promoter is a direct transcriptional target of PXR and contains two DR-3-type PXR response elements. Therefore, PXR can regulate CD36 directly, or indirectly through its activation of PPARγ .[23]

LXRs, both the α and β isoforms, were identified as sterol sensors that regulate cholesterol homeostasis.[39] Subsequent studies revealed that LXRs were also important regulators of fatty acid and glucose homeostasis. LXR agonists include endogenous cholesterol metabolites 24(*S*),25-epoxycholesterol, 24(*S*)-hydroxycholesterol and 22(*R*)-hydroxycholesterol,[40] as well as synthetic agonists, such as TO0901317 (TO1317) and GW3965.[41] LXRα is highly expressed in the liver, but its expression is also found in the adipose tissue, intestine, macrophages, lung and kidney. LXRβ is expressed ubiquitously.[42] LXRs regulate fatty acid synthesis in the liver[43–45] and treatment of mice with LXR agonists elevates triglyceride levels in the liver as well as in the plasma.[43,44] It was initially thought that the lipogenic activity of LXRs was mainly mediated through the activation of SREBP-1c, which can subsequently activate lipogenic enzyme genes, such as fatty acid synthase, SCD-1 and acetyl coA carboxylase 1.[43] But in a recent report, Zhou *et al.*[23] showed that LXR might also promote lipogenesis by activating the expression of CD36. Genetic (by using the VP-LXR transgene) or pharmacological (by using LXR agonists) activation of LXR induced the expression of CD36 by the binding of LXR to a LXR response element

(LXRE) in the CD36 gene promoter. Interestingly, similar to its regulation by PXR, CD36 regulation by LXR was also liver-specific. Further studies confirmed that the lipogenic effect of LXR and activation of CD36 was not a simple association, because the effect of LXR agonists on increasing hepatic and circulating levels of triglycerides and FFAs were largely abolished in CD36 knockout mice,[46] suggesting that intact expression and/or activation of CD36 is required for the steatotic effect of LXR agonists.

Aryl hydrocarbon receptor in fatty liver disease

Aryl hydrocarbon receptor and its role in xenobiotic metabolism

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that belongs to the basic helix-loop-helix/period-AhR nuclear translocator-single minded family of proteins.[47] AhR was originally isolated and characterized as a xenobiotic receptor sensing environmental toxicants, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) or dioxin.[48] For this reason, AhR is also called 'dioxin receptor'. AhR binds structurally diverse xenotoxicants, such as benzo[*a*]pyrene and 3-methylcholanthrene (3MC), as well as endobiotic chemicals, such as indigo and 6-formylindolo[3,2-*b*]carbazole. Industrial or military exposures to dioxin, such as those associated with the use of the herbicide and defoliant Agent Orange during the Vietnam War, have been linked to detrimental health effects. AhR is a central regulator of xenobiotic metabolism by inducing the microsomal cytochrome P450 1A and 1B genes. AhR also regulates the expression of several phase II glutathione *S*-transferase and UDP-glucoronosyltransferase enzymes. AhR heterodimerizes with AhR heterodimeric partner (ARNT) to regulate gene expression.[49,50] In the absence of ligand, AhR resides primarily in the cytoplasm as an inactive complex consisting of two 90-kDa heat-shock proteins (Hsp90), X-associated protein 2 (also known as AhR-interacting protein, or AIP) and Hsp90 co-chaperone protein p23.[51] The binding of a ligand to AhR triggers nuclear translocation and dissociation of Hsp90, AIP and p23, which subsequently allows AhR's heterodimerization with ARNT.[52] The AhR–ARNT complex then binds to dioxin responsive elements (DREs) in the promoter region of target genes. It is believed that AhR function mediates the adaptive response as a sensor to xenobiotic signals since it regulates a number of phase I and II enzymes. AhR is also a primary mediator of xenobiotic-induced toxicity, including cancer, immunosuppression, liver damage and birth defects. The relationship between AhR and toxic responses is well documented by the genetic ablation of AhR, which renders experimental animals resistant to dioxin or benzo[*a*]pyrene-induced toxicity.[53]

Although AhR was initially identified as a xenobiotic receptor, subsequent studies, mainly through the characterization of AhR knockout mice, have suggested that AhR also has endobiotic functions by affecting physiology and tissue development.[54–56] The endobiotic functions of AhR are also supported by the identification of endogenous AhR agonists, including modified LDL.[57]

An emerging role for AhR in fatty liver disease

Lee *et al.*[58] have recently reported the creation of tetracycline-inducible, constitutively activated, AhR (CA-AhR) transgenic mice. The constitutive activation was achieved by deleting the minimal ligand-binding domain (amino acids 287–422) of AhR, which allows constitutive dimerization with ARNT, binding to DREs and activation of AhR target genes.[59] These tissue- and temporal-specific transgenic mice represent a unique *in vivo* gain-of-function model to study AhR function *in vivo*. It is known that treatment with AhR ligands, such as TCDD, may exert systemic effects and may have additional transcriptional consequences independent of the presence of endogenous AhR.[58,60]

Compared with wild-type mice, CA-AhR transgenic mice exhibited spontaneous hepatic steatosis, manifested by the accumulation of triglycerides but not cholesterol in the liver. The steatotic effect of AhR was independent of SREBP-1c-mediated *de novo* fatty acid synthesis. Instead, the lipogenic effect of AhR likely resulted from its activation of CD36 gene expression and the consequent increase of hepatic FFA uptake. Activation of CD36 gene expression was observed in both CA-AhR transgenic mice and TCDD-treated wild-type mice, and both mouse and human CD36 gene promoters were established as direct transcriptional targets of AhR.[58] In addition to CD36, the expression of FATP1 and FATP2, which can also facilitate hepatic FFA uptake, was increased in CA-AhR transgenic mice. The activation of CD36 gene expression in transgenic mice was associated with an increase in fatty acid uptake in hepatocytes. Moreover, the steatotic effect of an AhR agonist was abrogated in CD36 knockout mice.

In the transgenic model, the effect of the CA-AhR transgene was most likely hepatocyte-specific because the promoter was expected to target hepatocytes only. However, in the pharmacological model and in AhR null mice, we cannot exclude the possibility that the expression and/or regulation of CD36 in Kupffer cells and hepatic stellate cells might have also played a role in the steatotic phenotype. Activation of AhR appeared to have pleotropic effects on steatosis. In addition to the activation of CD36 gene expression, pharmacological activation of AhR also inhibited VLDL-triglyceride secretion. The reduced VLDL secretion was associated with a decreased plasma protein level of ApoB100, but not ApoB48. The peroxisomal fatty acid β-oxidation was also inhibited in CA-AhR transgenic mice. The expression of the rate-limiting enzyme of peroxisomal β-oxidation, acyl coenzyme A oxidase1 (ACOX1), was suppressed in CA-AhR transgenic mice. Adipose lipolysis was probably increased as suggested by the increased expression of adipose triglyceride lipase mRNA in CA-AhR transgenic and TCDD-treated mice.

In an independent study, Kawano *et al.*[61] showed that 3-methylchoranethrene (3-MC), another AhR agonist, induced hepatic steatosis through a similar mechanism.

Treatment with 3-MC significantly enhanced the expression of CD36 in mice and in cultured human hepatoma HepG2 cells. Treatment of mice with 3-MC changed the expression of key transcription factors involved in lipid metabolism, including PPARα and SREBP-1. It is interesting to note that 3-MC-mediated induction of PPARα, a positive regulator of CD36, was not observed in CA-AhR transgenic mice. Nevertheless, studies from several laboratories have clearly demonstrated a novel link between AhR-induced steatosis and the expression of CD36.

Summary and perspectives

Recent studies, as summarized in Figure 1, have established the role of CD36 and its regulation by AhR and nuclear receptors in the pathogenesis of hepatic steatosis. The shared regulation of CD36 by AhR and nuclear receptors PXR, LXR and PPARγ suggests FAT as a common target of these receptors in their control of lipid homeostasis. As xenobiotic receptors, the primary function of AhR and PXR is xenobiotic response by regulating the expression of drug metabolizing/detoxifying enzymes and transporters. The regulation of CD36 by AhR and PXR suggests that in addition to their xenobiotic functions, these two receptors can also impact the homeostasis of endobiotics, such as the lipids. LXR was previously known for its lipogenic activity through the activation of Srebp-1c and several key lipogenic enzymes. The regulation of CD36 by LXR suggests a novel mechanism by which LXR may affect lipid metabolism.[23] PPARγ was previously known to activate the expression of CD36 in macrophages, which was implicated in foam cell formation and atherosclerosis.[38] The more recent results suggested that the regulation of CD36 by PPARγ is conserved in hepatocytes, and in addition to its direct transactivation of CD36, PPARγ could also mediate the effect of PXR on CD36 gene expression by functioning as a PXR target gene.[23]

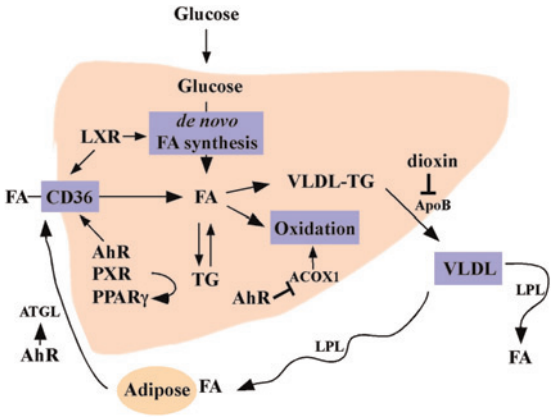

Figure 1 Summarized function of CD36 and its regulation by AhR and nuclear receptors in hepatic lipid homeostasis. AhR and its ligand have pleotropic effects on AhR gene expression and lipid metabolism. The expression of CD36 is also regulated by several nuclear receptors, such as PXR, PPARγ and LXR. The shaded area indicates hepatocytes. Increased CD36 expression promotes fatty acid uptake and subsequently leads to triglyceride accumulation within the hepatocytes. In addition to CD36 induction, AhR activation also inhibits peroxisomal fatty acid β-oxidation through the suppression of ACOX1. AhR agonists, such as dioxin, decrease VLDL-triglyceride secretion by reducing the plasma level of ApoB100. Activation of AhR also has extrahepatic effects, such as the induction of ATGL and promotion of peripheral fat mobilization. ACOX1, acyl coenzyme A oxidase 1; AhR, aryl hydrocarbon receptor; ATGL, adipose triglyceride lipase; FA, fatty acids; LPL, lipoprotein lipase; LXR, liver X receptor; PPARγ, peroxisome proliferator-activated receptor γ; PXR, pregnane X receptor; TG, triglycerides; VLDL, very low-density lipoprotein (A color version of this figure is available in the online journal)

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CD36 is previously known for its functions in macrophages, endothelium and smooth muscle cells. The network of CD36 regulation in the liver underscores the previously unrecognized significance of CD36 in the liver. Liver plays an important role in insulin-mediated fat and glucose metabolism. It remains to be determined whether AhR has a broader role in impacting obesity and diabetes. Indeed, adiposity was decreased in CA-AhR transgenic mice, but this was likely due to an indirect mechanism, because the transgene was not targeted to the adipose tissue. In addition, AhR may have direct effects on adipogenesis since it has been reported that NF-E2 p45-related factor 2 (NRF2) inhibited adipogenesis through activation of AhR.[62]

Exposure to dioxin or polychlorinated biphenyls has been linked to insulin resistance and diabetes. Dioxin exposure was associated with increased prevalence of fatty liver in human populations.[63] Although the regulation of CD36 by AhR has been shown to be conserved in human liver cells,[58,61] the human relevance of CD36 in the pathogenesis of fatty liver needs to be systemically evaluated.

Simple steatosis or NAFLD, if unmanaged, may progress into NASH. Recent reports suggest that CD36 and other surface receptors may play a role in the pathogenesis of NASH by affecting Kupffer cells or hepatocytes. Bieghs and colleagues showed that transplantation of LDLR knockout mice with bone marrow from SRA and CD36 double-knockout mice reduced diet-induced hepatic inflammation, apoptosis, lipid oxidation and fibrosis, which are common features of NASH. The hepatocyte-specific CA-AhR transgenic mice showed signs of oxidative stress and inflammation.[58] It remains to be determined whether the hepatic steatosis observed in CA-AhR transgenic mice may eventually progress to NASH, or activation of AhR will sensitize animals to NASH.

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