REVIEWS

PPARα and NCOR/SMRT corepressor network in liver metabolic regulation

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Abstract
Peroxisome proliferator-activated receptor alpha (PPARα, NR1C1) belongs to a large family of ligand-dependent nuclear receptors (NRs). It is one of the best studied NRs which controls the lipid metabolism (mainly fatty acid oxidation) and inflammation, and has been a promising target for treating metabolic disorders such as fatty liver and cardiometabolic diseases. The function of PPARα relies on its interaction with various coregulators upon different stimulating contexts, and, thereby, activates or represses its transcription targets in a gene-selective manner. Understanding the transcription factor and coregulator network underlying the PPARα regulation is prerequisite to decipher its gene- and context-selectivity for designing better therapeutic ligands. In this review, we will summarize current knowledge of PPARα coregulator network, with major focus on a relatively well-studied corepressor complex containing core subunits of nuclear receptor corepressor (NCOR or NCOR1), silencing mediator of retinoic acid and thyroid hormone receptor (SMRT or NCOR2), G-protein suppressor 2 (GPS2), transducin β-like protein 1 (TBL1 or TBL1X), TBL-related 1 (TBLR1 or TBL1XR1), and the catalytic core of histone deacetylase 3 (HDAC3).

We will mainly review the molecular events of the complex and sub-complexes in controlling the liver metabolism. We will also discuss the potential perturbation of

Abbreviations: AA, amino acid; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette sub-family G member 1; AF, activation function; AKT, protein kinase B (alias PKB); ATGL, adipose triglyceride lipase; BCL6, B-cell lymphoma 6; CBP, CREB-binding protein; CDK5, cyclin-dependent kinase 5; CGID, corepressor and G-protein suppressor 2 interacting domain; ChIP, chromatin immunoprecipitation; CoRNR, corepressor-nuclear receptor; CPT1, Carnitine palmitoyl transferase 1; CYP7B1, 25-hydroxycholesterol 7-alpha-hydroxylase; DAD, deacetylase-activation domain; DBD, DNA-binding domain; FGE21, fibroblast growth factor 21; FXR, farnesoid X receptor; GABP, GA-binding proteins; GPS2, G-protein suppressor 2; GR, glucocorticoid receptor; HAT, histone acetyltransferase; HDAC3, histone deacetylase 3; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; HSL, hormone-sensitive lipase; KDM4A, Lysine-specific demethylase 4A; LBD, ligand-binding domain; LPS, lipopolysaccharides; LRH-1, liver receptor homologue-1; LXR, liver X receptor; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; NAFLD, non-alcoholic fatty liver diseases; NASH, non-alcoholic steatohepatitis; NCOR, nuclear receptor corepressor (alias NCOR1); NGS, next generation sequencing; NRs, nuclear receptors; PDK4, Pyruvate dehydrogenase lipoyamide kinase isozyme 4; PIASy, protein inhibitor of activated STAT protein gamma (alias PIAS4); PI3K, the class 3 phosphoinositide-3-kinase; PPAR, Peroxisome proliferator-activated receptor; PPRE, PPAR response element; RAR, retinoic acid receptor; RD, repressor domain; RID, NR interaction domains; SANT, SWI3/ADA2/NCoR/TFIIIB; SHP, small heterodimer partner; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor (alias NCOR2); SNP, single nucleotide polymorphism; SRC1, steroid receptor coactivator-1; S6K2, S6 kinase 2; TBL1, transducin β-like protein 1 (alias TBL1X); TBLR1, transducin β-like protein-related 1 (alias TBL1XR1); TNFα, tumor necrosis factor alpha; TR, thyroid hormone receptor; TSC1, tuberous sclerosis proteins 1; TZD, Thiazolidinedione; UBC9, ubiquitin-conjugating enzyme E2; VPS15, PI3K regulatory subunit 4 (alias PI3KR4).

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the subunit expression in human livers during liver metabolic disorder progression which potentially defines the patient disease susceptibility and drug responses.

**KEYWORDS**
coregulators, liver metabolism, NCOR, nuclear receptors, PPAR

### INTRODUCTION

Liver is the major organ for glucose and lipid metabolism. The regulation of those metabolic processes is controlled by transcription factors and coregulator networks. Perturbation of the transcriptional balance in the liver leads to dysregulated metabolism and triggers initiation of liver metabolic disorders such as non-alcoholic fatty liver diseases (NAFLD). More than 1500 transcription factors, dozens of them have been discovered to be closely linked with liver lipid and cholesterol metabolism. Of particular interest is the nuclear receptor (NR) superfamily of transcription factors. NRs have been intriguing the drug targets as their activities can be manipulated using specific ligands, either endogenous (ie, fatty acids, bile acids, steroid hormones) or synthesized compounds (such as fibrates and Thiazolidinediones-TZDs).

Among the 48 NRs identified in humans, the Peroxisome proliferator-activated receptors (PPARs) are the major regulators of liver lipid metabolism with proved clinical value. Three subtypes of PPARs, including PPARα, β/δ, and γ, have been identified. In contrast to PPARγ which is functionally divergent, both PPARα and β/δ control fatty acid β-oxidation. This functional diversity parallels with the tissue distribution of those subtypes. PPARα and β/δ are mainly expressed in tissues with high fatty acid β-oxidation level, while PPARγ is predominantly expressed in white adipose tissues to control adipocyte differentiation and lipogenesis. Both PPARα and γ agonists have been clinically applied for treating metabolic disorders. The PPARα agonists such as fibrates are used to treat hypertriglyceridemia patients, while PPARγ activating TZDs are widely applied for treating type 2 diabetes (T2D). There have been big ongoing efforts to identify more specific PPAR agonist(s) for better clinical applications. Most of the PPARα-targeting drugs are for T2D and dyslipidemia. Multiple mono- (ie, ZYH-7 for dyslipidemia), dual- (ie, PPARα/β Elafibranor, for NAFLD, T2D and dyslipidemia), or tri- (ie, Chilitazar for T2D) agonists are under clinical trials. There have been many failures in the PPARα trials, largely due to the side effects caused by its wide-spectrum of tissue and transcriptome targets. To achieve this, better understanding of the molecular mechanisms underlying PPARα coregulator network is required.

PPARα activity is regulated in the genomic level by coregulator networks. Upon signal stimulus, there is a conformational change of PPARα which triggers release the of corepressors and recruitment of coactivator complexes. These structural alterations activate PPARα and its downstream transcription (Figure 1). More than 350 coregulators have been identified to date. Above all, the corepressor complex composed of core subunits of nuclear receptor corepressor (NCOR or NCOR1), silencing mediator of retinoic acid and thyroid hormone receptor (SMRT or NCOR2) and the catalytic core of histone deacetylase 3 (HDAC3), is among the most studied PPARα regulators in different stimulus and disease contexts. Additional components of the corepressor complex include G-protein suppressor 2 (GPS2), transducin β-like protein 1 (TBL1 or TBL1X), TBL-related 1 (TBLR1 or TBL1XR1). The corepressor complex deacetylates the histones in the chromatin and thereby maintains the genome in poised status. This was discovered in both metabolic and inflammatory gene loci. The physical interaction of PPARα with the core subunits of this corepressor complex was first identified using yeast-two hybrid screening in the liver cDNA libraries. The NCOR/SMRT/HDAC3 corepressor has a large NR-binding surface, which allows interaction with multiple NR targets at the same time. Deletion of each corepressor subunit leads to phenotype changes related with various NR regulation. In addition, corepressor component expression in different disease stages might also define the patients’ susceptibility and drug responsiveness during disease progression. Understanding of the co-regulator network has been largely increased due to the development of cistromic analysis tools (ChIP-seq). In this review, we will mainly focus on the PPARα and corepressor interplay in regulating liver metabolism and their physiological relevance.

#### 1.1 Structure basis of PPARα and NCOR/SMRT corepressor complex

PPARα was the first subtype identified as a target of nafenopin, a hepatocarcinogen which causes peroxisome proliferation. Later studies confirmed that PPARα activation was associated with increased fatty acid β-oxidation. PPARα target genes have been identified through a group of genome-wide analysis, as systemically summarized previously. Depletion of PPARα in the liver caused defects in lipid metabolism and sensitized the mice to different dietary and inflammatory challenges. Despite that
three subtypes of PPARs share high level of homology, they have largely differential ligand specificities and functionalities.\textsuperscript{26,30} The ligand- and gene-selectivity of PPAR\(\alpha\) is defined in the structure level, similar to most of the other NRs. PPAR\(\alpha\) has six functional domains (Figure 2), namely the N-terminus activation function-1 (AF-1) or A/B domain, the DNA-binding domain (DBD or C), a hinge domain (D) and the C-terminus ligand binding domain (LBD)/AF-2 or E/F domain. The function of the four PPAR\(\alpha\) domains was reviewed in detail previously.\textsuperscript{7} The A/B domain can be phosphorylated and confers both ligand-dependent and independent transactivation functions of PPAR\(\alpha\). It also defines the transcription target profiles among different NRs. The DBD domain contains two zinc-finger structures that recognize and bind to PPAR response elements (PPREs) in the target genes (Figure 2).

NCOR and SMRT are structurally similar and contain several conserved functional domains.\textsuperscript{17} NCOR and SMRT share identical N-terminus repressor domains (RDs) (Figure 3A,B). The NCOR and SMRT RD1 domain contains conserved coiled-coil region (AA161-AA225 for NCOR and AA151-AA217 for SMRT) that is required for both GPS2 and TBL1/TBLR1 interaction.\textsuperscript{31} GPS2 uses its N-terminus coiled-coil region (AA1-AA105) to interact with the RD1 domains of NCOR (Figure 3A,C) and SMRT,\textsuperscript{31} with minimum peptides of AA1-AA60 to interact with SMRT\textsuperscript{13} (Figure 3B,C). The AA1-AA70 in the N-terminal region of GPS2 binds to the corepressor and GPS2 interacting domain (CGID) of TBL1 (Figure 3D). GPS2 and SMRT thus forms anti-parallel interaction with TBL1 in the corepressor complex (Figure 3E). Interestingly, TBL1 was able to protect the GPS2/SMRT complex from proteolysis, suggesting its
potential regulatory role in the complex stability in vivo. The RD1 domain of NCOR and SMRT is followed by deacetylase-activation domain (DAD) that consists of two SWI3/ADA2/NCoR/TFIIIB (SANT) regions (AA440-AA674 for NCOR and AA395-AA763 for SMRT). SANT1, along with its N-terminus flanking sequences are both required for HDAC3 recruitment and activation. In consistence, isolated HDAC3 is enzymatically deficient without DAD of either NCOR or SMRT.

The C-terminus of NCOR and SMRT has two NR interaction domains (RIDs). The RIDs use the CoRNR boxes (containing the NR-interaction motifs) to interact with agonist- or antagonist-binding NRs such as PPARα (Figure 3A, B and E). GPS2 binds to PPARα through AA100-AA155 which locates after the coiled-coil domain and is separated from the GPS2/NCOR (SMRT) interaction domains (Figure 3C). As NCOR interacts with GPS2 through the N-terminus RD1 domain, it is likely that GPS2 works to stabilize NCOR/PPARα complex. Indeed, interaction of NCOR with PPARα was much stronger in presence of GPS2 in 293 cells. Although PPARα physically binds to TBL1 and TBLR1 in GST-pull down assays, the exact regions and the structural basis for their interplay have not been solved yet. HDAC3 is the core catalytic subunit of the corepressor complex and its deacetylase activity depends on the NCOR/SMRT. It is likely that NCOR and GPS2 repress PPARα by further recruiting HDAC3 in the chromatin level. Direct interaction of HDAC3 and PPARα has not been reported, despite that earlier studies showed interplay of the two components in the chromatin level to regulate fibroblast growth factor 21 (FGF21) in the HepG2 cells.

Conclusively, NCOR/SMRT/GPS2 complex physically interacts with PPARα and inhibits its active conformational changes, while TBL1/TBLR1 bind to and act as PPARα coactivators.

1.2.1 | NCOR/SMRT are identified as PPARα-interacting corepressors

NCOR and SMRT are large proteins (around 270 kd) that share homology of around 43%. NCOR and SMRT were first identified as strong NR (retinoic acid receptor-RAR and thyroid hormone receptor-TR)-interaction proteins through unbiased yeast two-hybrid screening experiments. The binding of NCOR and SMRT to the NRs leads to repressed NR activity. It was soon clear that in addition to TR and RAR, NCOR and SMRT repress multiple other NRs due to their large protein size and binding surface. The first study to report involvement of NCOR in PPARα signaling pathway was published in 1999. In this study, the authors used the C-terminus RID domain of NCOR as a bait in the yeast two-hybrid screening experiment to fish for its interaction partners.
PPARα strongly interacted with NCOR RID domain and such interaction was dose-dependently decreased by PPARα ligand WY-14643. In addition, NCOR binding to RARγ was also abolished by 9-cis-RA. In contrast, the interaction of PPARα with coactivator P300 showed an opposite trend in response to ligands. Further investigation in the PPARα and corepressor structure confirmed the details of this functional interplay. PPARα LBD domain contains 13 α-helices and 4 β-strands which forms into a helical sandwich structure composed of a large T-shaped cavity. The binding of its ligand leads to stabilization of the helix in the AF-2 region. This promotes the recruitment of the coactivator recognition region (the LXXLL peptide from both steroid receptor coactivator-1 or SRC1 and CREB-binding protein or CBP) to the hydrophobic cleft on the surface of PPARα, leading to its activation. In presence of the corepressor NR-interacting motifs (the LXXI/HXXXLI, both in NCOR and SMRT), the three-turn α-helix of the peptide docks into the helices of the PPARα LBD region. The peptide also extends to the AF-2 helix to prevent it from forming the activation conformation. The corepressor interaction interface is larger than the coactivators. This partially explains the preference of PPARα binding to corepressors in poised (unliganded) conditions. In consistence, both NCOR and SMRT inhibited PPARα activity in the cell lines (HEK293 cells). As all three PPAR sub-family proteins share homology in the hinge regions (implicated in corepressor recruitment), NCOR and SMRT were reported to repress both PPARβ/δ and PPARγ.

1.2.2 PPARα posttranslational modifications control its inhibitory functions through NCOR corepressor complexes

Posttranslational modifications affect PPARα activity via controlling the recruitment of corepressors (Figure 2). The K185 in the hinge domain of PPARα can be SUMOylated by protein inhibitor of activated STAT protein gamma (PIASg or PIASy) and ubiquitin-conjugating enzyme E2 (UBC9) complex. K185 SUMOylation was dose-dependently decreased by PPARα ligand GW7647, and was required for PPARα binding to NCOR. As a result, the PPARα target genes such as fatty acid metabolic genes of Pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK4) and Carnitine palmitoyltransferase 1 (CPT1) were maintained in the repression state in the Huh7 human liver cell line (Figure 4A). Interestingly, K185 SUMOylation was specific to PPARα/NCOR but not SMRT recruitment as the SMRT-specific genes were not affected by the K185R mutant, the underlying structural basis is not cleared yet. In another study, Leuenberger et al proposed that the K358 in the mouse PPARα LBD region was crucial for the ligand-dependent repression of a cholesterol metabolic gene 25-hydroxycholesterol 7-alpha-hydroxylase (Cyp7b1) in the liver (Figure 4B). Mechanistically, SUMOylation of K358 promoted the recruitment of GABPs, NCOR, and HDAC corepressor complex. The GABP/NCOR/HDAC complex induced DNA methylation in the Cyp7b1 promoter and inhibited its transcription. In contrast to the K185 SUMOylation,
K358 SUMOylation was enhanced by PPARα ligand treatment, thus was consistent with its repressive function in the Cyp7b1 gene.44

In addition to SUMOylation, PPARα could also be phosphorylated at S12 and S21 of AF1 region by mitogen-activated protein kinase (MAPK) upon insulin stimulation in HepG2 human liver cell line. Phosphorylation at both sites abolished NCOR and SMRT recruitment. It is likely that phosphorylation of both sites changed the structure of PPARα, which destabilized the interaction of its hinge domain with NCOR/SMRT corepressor complex.45

It is also plausible that the corepressors themselves contribute to the NR posttranslational modifications. For example, NCOR promoted PPARγ phosphorylation at S273 in the mouse adipocytes by recruiting CDK5 to the PPARγ. This maintained PPARγ in the repressed status. Deletion of NCOR in mouse adipocytes, therefore, created a constitutively activated PPARγ, leading to enhanced adipogenesis and insulin sensitivity in obese mouse models.46 Similar observation was not yet reported in PPARα LBD regions.

1.2.3 | NCOR posttranslational modifications define its NR preference

Intriguingly, insulin modulated phosphorylation of NCOR (S1460) in the RID regions via AKT-dependent mechanism.47 S1460 phosphorylation of NCOR largely affected its NR binding preference, specifically from the lipogenic liver X receptor alpha (LXRα) to the fatty acid oxidative PPARα. As a result, insulin caused derepressed LXRα activities in the liver which led to liver steatosis (Figure 4C).47 As NCOR and SMRT have much larger domains than the NRs, they can be modified by different kinases.48 Signal-dependent posttranslational modifications and their effects on corepressor NR preference might represent an interesting mechanism linked to different human diseases.

1.2.4 | Nutrient deprivation and nourishment regulate PPARα activities through NCOR

Nutrient deprivation induces lysosomal degradation and autophagy.49 Increased autophagy in the liver selectively degrades NCOR and HDAC3, possibly via Atg8-like proteins in the lysosomes in the liver.50 Hepatocyte-specific deletion of autophagy related 5 (Atg5) or Atg7 in mice showed phenotypes of defective conventional autophagy and dampened fatty acid oxidation in the liver.51 These phenotypes were associated with NCOR accumulation in the hepatocytes in those mice, which inhibited the liver PPARα activities.51 Autophagy is regulated by the class 3 phosphoinositide 3-kinase (PI3K).50 Depletion of the Vps15 subunit of PI3K in the mice liver impaired liver autophagy. As a result, nuclear NCOR and HDAC3 were accumulated and subsequently inhibited PPARα and fatty acid metabolic pathways in the liver.50

The mammalian target of rapamycin (mTOR) is the key transcription factor in nutrient regulatory network.49,52,53 Deletion of the mTOR complex 1 (mTORC1) inhibitor tuberous sclerosis proteins 1 (TSC1) in the mouse liver caused defects in fasting-induced ketogenesis which was similar to aging.53 And this function was PPARα-dependent and was related with S6 kinase 2 (S6K2), a downstream effector of the mTORC1. S6K2 interacted with both PPARα and NCOR. Phosphorylated S6K2 then served as an adapter to bring NCOR to PPARα in the liver cell nucleus to inhibit PPARα target gene expression (Figure 4D).54 The repressed PPARα activity in the feeding condition might also be related with other corepressors such as B-cell lymphoma 6 (BCL6), which promoted the recruitment of the NCOR/HDAC3 complex to repress PPARα target genes in the liver.55

These findings beautifully explained how nutrient deprivation controls lipid metabolism via corepressor-based mechanisms.

1.2.5 | In vivo functions of NCOR and SMRT discovered from mouse models

Both NCOR and SMRT have multiple NR targets. A group of mouse models have been generated to study the physiological functions of NCOR and SMRT in vivo (Figure 5 and Table 1). Transgenic mice with liver-specific expression of NCORi (a mutant with ablated N-terminus RD domain) was generated. The truncated NCOR still bound to TR but
was not able to recruit the corepressor complex, therefore, it competed the endogenous TR with the functional NCOR. The NCORi transgenic mice had increased hypothyroid response but did not show changes in hyperthyroid conditions. Another study from the same group deleted two RID domains of NCOR (proximal to the N-terminus) observed similar effects that in both hypothyroid and euthyroid conditions, the TR response is derepressed. It was also observed that in those mice, a group of LXR target genes (ie, Srebp1, Pltp, Abca1, etc) were also increased (Note that both Pltp and Abca1 are also classical PPARα target genes). A more interesting finding in the macrophage-specific NCOR KO mice was that deletion of NCOR enhanced anti-inflammatory unsaturated fatty acid synthesis and secretion from the macrophages, and those lipids contributed to the metabolically protective roles in the obese mouse models. The derepressed unsaturated fatty acid pathway was related with LXRα. Those studies and many others have confirmed that the RID domain of NCOR is important to regulate the functionality of multiple NRs in vivo.

### Table 1: Phenotypes in NCOR and SMRT-related mouse models

| Protein | Mouse model | Phenotypes | TFs | Ref |
|---------|-------------|------------|-----|-----|
| NCOR Global KO | • Embryonic lethal • CNS, erythrocyte, and thymocyte defects | TR | [68] |
| Liver Alb-NCORi transgenic | • Derepressed TR-activated genes in basal but not liganded conditions • Increased hepatocyte proliferation | TR, LXR | [56] |
| Liver NCOR RID knockout | • Derepressed TR-activated genes in hypothyroid and euthyroid conditions • Activation of LXR target genes • Improved dietary cholesterol tolerance due to diminished intestinal cholesterol absorption | TR, LXR | [57, 58] |
| Global NCOR RID knockout | • Low T4 and T3 levels • Sensitized peripheral TR responses • Improved insulin resistance in TRβ deficient mice | TR | [69, 70] |
| Global NCOR DADm knockin | • Reduced body weight and increased energy expenditure. • More insulin sensitive • Derepressed TR response in hypothyroid and euthyroid conditions • Dysregulated circadian clock genes | RevErb, TR | [71, 72] |
| LKO (AAV-TBG-Cre injection) | • Increased lipogenesis and liver steatosis • Reduced liver glycogen content | – | [73] |
| LKO (Alb-Cre) | • Reduced fasting lipogenesis • Reduced fatty acid oxidation and ketogenesis in feeding • Increased liver regeneration after partial hepatectomy • Alleviated diethyl nitrosamine (DEN)-induced liver cancer development • Liver steatosis | PPARα, ERRα, LXRα, TR | [64, 74, 75] |
| SMRT Global KO | • Embryonic lethal • Forebrain and neuron developmental defect | – | [76] |
| Global SMRT mRID knockin | • Reduced energy expenditure • Altered insulin sensitivity • 70% increase in adiposity | TR, PPARγ | [63] |
| Global SMRT mRID1 knockin | • Impaired mitochondrial function and oxidative stress • Obesity, insulin resistance, adipocyte hypertrophy, liver steatosis and impaired thermogenesis and mitochondrial biogenesis in brown adipose tissue (BAT) due to defected OxPhos | PPARα,σ and γ, TR and RAR | [60, 61] |
| LKO (AAV-TBG-Cre injection) | • No obvious liver phenotypes | – | [73] |
| LKO (Alb-Cre) | • No obvious liver phenotypes • Unchanged TR responses | – | [64] |
The RID domains NR preference was studied. NCOR and SMRT RID2 is the RID domain that preferentially interacts with PPARs. An interesting global SMRT RID1 (SMRT\textsuperscript{Mrid1}) KO mouse model was generated.\textsuperscript{60} The rational was that ablation of one RID domain dissected its function from the other via more specific NR selectivity (Figure 5 and Table 1). Indeed, the SMRT\textsuperscript{Mrid1} mice showed insulin resistance, adipocyte hypertrophy and inflammation, liver steatosis accompanied by reduced thermogenesis and mitochondrial dysfunction in brown adipose tissues, upon high-fat diet (HFD) challenges (Table 1).\textsuperscript{61} The reduced OXPHOS gene expression and mitochondrial functions in multiple organs due to repressed PPAR activities.\textsuperscript{60} In consistence with this, PPAR\(\alpha\), \(\delta\) and \(\gamma\) target genes were downregulated in major metabolic organs, confirming the functional importance of PPAR/SMRT RID2 complex in regulating energy metabolism in vivo (Table 1).\textsuperscript{60} Single nucleotide polymorphisms (SNPs) close to the SMRT RIDs coding regions were also observed in humans and related with T2D.\textsuperscript{60} Noteworthy, a natural SNP of V227A in PPAR\(\alpha\) coding regions were also observed in humans and related nucleotide polymorphisms (SNPs) close to the SMRT RID domains, leading to repressed PPAR\(\alpha\) activity in 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2, a rate-limiting enzyme in the fatty acid oxidation pathway) promoter and caused hyperlipidemia.\textsuperscript{62}

In contrast, disruption of two RID domains of SMRT (SMRT\textsuperscript{Mrid}) in mice led to global metabolic defects.\textsuperscript{63} The mutation caused respiration reduction, altered insulin sensitivity and 70% increase in adiposity in mice, due to derepressed PPAR\(\gamma\) and drastically accelerated adipocyte differentiation (Figure 5 and Table 1).\textsuperscript{63}

Despite that NCOR and SMRT both repress PPAR activities, deletion of each in the liver showed very different phenotypes. Liver-specific NCOR KO mice had spontaneous steatosis (Table 1)\textsuperscript{64} similar to HDAC3 KO mice.\textsuperscript{65,66} In contrast, the liver-specific SMRT KO mice showed no liver steatosis (Table 1).\textsuperscript{64} Also, NCOR but not SMRT seems to be the major modulator of TR\textsuperscript{67} and many other NRs (such as Rev-erbs\textsuperscript{65}) in the liver, although global deletion of SMRT causes body weight gain\textsuperscript{67} (potentially related with derepressed metabolic and inflammation pathways in other metabolic tissues such as adipocytes and tissue macrophages\textsuperscript{19,20}). Investigation into the transcriptomics in NCOR, SMRT, or double-KO mice revealed transcriptomic signatures annotated to PPAR\(\alpha\) signaling pathways in NCOR but not SMRT KO mice (Table 1).\textsuperscript{20,64} The major reason of this tissue-specific corepressor function remains ambiguous and requires further investigation.

To summarize, NCOR but not SMRT is involved in PPAR\(\alpha\) regulation in the liver. It also controls liver metabolism by repressing multiple metabolic NRs in vivo.

### 1.3 | Multi-functional regulation of HDAC3 in liver metabolism and its involvement in PPAR\(\alpha\) signaling

The enzymatic activity of HDAC3 requires NCOR in the liver.\textsuperscript{73} As HDAC3 is the core functional component in the NCOR/SMRT corepressor complex,\textsuperscript{77} it is in theory natural that HDAC3 is involved in NCOR/PPAR pathways. As a result, although direct interaction of HDAC3 with PPAR\(\alpha\) is not reported, it does not exclude the possibility that PPAR\(\alpha\) and HDAC3 interplay in the chromatin level, via the NCOR/SMRT corepressor complex. Noteworthy, HDAC3 was reported to directly interact with and acetylate PPAR\(\gamma\) to blunt TZD response in the adipocytes in mice.\textsuperscript{78} The inhibitory function of HDAC3 on PPAR\(\gamma\) was also reinforced via its nucleus translocation promoted by I\(\kappa\)B\(\alpha\), partially explaining the mechanism how tumor necrosis factor alpha (TNF\(\alpha\)) inhibited the PPAR\(\gamma\) activities.\textsuperscript{79} As a result, HDAC inhibitors improved insulin sensitivity in early studies.\textsuperscript{80} In consistence, a recently published paper found that deletion of HDAC3 in the intestine led to upregulation of both mitochondrial and peroxisomal \(\beta\)-oxidation due to derepressed PPAR\(\alpha\) in the intestinal epithelial cells. This was related with improved insulin resistance in obese mouse models.\textsuperscript{81} In addition, response of those cells to PPAR\(\alpha\) agonist was sensitized in the KO mice.\textsuperscript{81}

#### 1.3.2 | HDAC3 interplays with PPAR\(\alpha\) in the liver.

The direct connection of HDAC3 and PPAR\(\alpha\) in the liver was not sufficiently studied. In aging (21 months old) mice, the occupancy of HDAC3 was colocalized with PPAR\(\alpha\) (also PPAR\(\gamma\) and LXR\(\alpha\)) in a subset of lipogenesis genes that led to liver steatosis.\textsuperscript{82} An interesting study published very recently reported that deletion of PI3K subunit Vps15 inhibited PPAR\(\alpha\) activity due to recruitment of NCOR and HDAC3, and inhibition of HDAC3 in the hepatocytes rescued the PPAR\(\alpha\) responses.\textsuperscript{80} This further supports the interplay of PPAR\(\alpha\) and HDAC3 in mouse hepatocytes.

In accordance with these findings, an early study in the human liver HepG2 cells reported that treatment of the cells with sodium butyrate, a class I HDAC inhibitor (targets mainly HDAC1, 2 and 3) enhanced the expression of FGF21. This elevation was related with disrupted interaction of PPAR\(\alpha\) and HDAC3 in the FGF21 promoter level.\textsuperscript{34} FGF21 is a PPAR\(\alpha\) regulated cytokine and liver is one of its major sources.\textsuperscript{83-87} FGF21 promotes liver fatty acid oxidation and improves metabolic dysregulation in obesity.\textsuperscript{88}
However, the liver-specific HDAC3 KO mice had no elevation in liver Fgf21 expression and showed severe liver steatosis.65 It was later known that the circadian regulating NR RevErbs were the major targets of HDAC3 in the liver. RevErbα recruits NCOR and HDAC3 to repress target gene expression and such function likely over-writes the effects of PPARα in the physiological conditions.65 Indeed, both liver NCOR and RevErbKO mice showed liver steatosis phenotype, resembling that of the liver HDAC3 KO mice.57,89

As the catalytic core of the corepressor complex, HDAC3 interplays with PPARα (and multiple other NRs) in the chromatin level to control liver metabolism.

1.4 | TBL1 and TBLR1 and the corepressor/coactivator switch mechanisms in liver metabolism

1.4.1 | TBL1 and TBLR1 are coactivators of PPARα in the liver

TBL1 and TBLR1 are regulatory components of the NCOR/SMRT corepressor complex. Both can interact with NCOR/SMRT and GPS2 via different domains.13 Its presence protects the SMRT/GPS2 complex from proteolysis in the purified proteins. In the obese mouse models, TBL1 but not TBLR1 mRNA expression in the liver was downregulated. In addition, the TBL1 mRNA level was significantly correlated with the liver triglyceride level in human donors.23 Knocking down either TBL1 or TBLR1 using adenovirus shRNA in the mouse liver reduced fasting ketogenesis and increased lipid accumulation.23 In consistence, knocking down both TBL1 and TBLR1 in leptin receptor KO db/db mice further promoted liver steatosis while over-expression of TBL1 and TBLR1 had opposite effects. Further investigation revealed that TBL1 and TBLR1 worked as coactivators of PPARα and were both required for PPARα regulation of fatty acid oxidation and ketogenesis.23 These findings challenged current understandings that TBL1 and TBLR1 are regulatory components of the NCOR/SMRT corepressor complex.90

1.4.2 | A corepressor/coactivator switch mechanism of TBL1 and TBLR1

The functions of TBL1 and TBLR1 as corepressors were confirmed in earlier studies, as they both inhibited TR activities in the hypothyroid condition, which was in accordance with the role of NCOR.90 However, another study in the embryonic stem cells reported that knocking down of TBL1 severely impaired the PPARα activation and halted the adipogenesis in those cells. More interestingly, TBLR1 was found to be required for the switch of corepressors (NCOR/SMRT) to coactivators upon ligand activation. And such corepressor/coactivator exchange mechanisms seemed to operate also for inflammatory transcription factors such as c-Jun and NFκB.91 This mechanism might explain the TBL1/TBLR1 in the PPARα pathways. Noteworthy, recent studies using advanced sequencing techniques also identified corepressors (NCOR and HDAC3) in the activation chromatin loops.92 The functional and mechanistic role of those corepressors in the assembly and activation of 3D chromatin structures remains largely ambiguous.

In conclusion, TBL1 and TBLR1 may serve as transit proteins to control switch of corepressors to coactivators, which might explain their coactivator behaviors in the liver PPARα pathways.

1.5 | The metabolic role of GPS2 as a coregulator of PPARα and other NRs

1.5.1 | GPS2 is a PPARα corepressor and inhibits fatty acid oxidation in the liver

GPS2 was first identified as PPARα coregulator by yeast two-hybrid screening from human liver cDNA library using PPARα as a bait.22 Subsequent studies revealed GPS2 as a regulatory component of the NCOR/SMRT corepressor complex and was mainly found to inhibit inflammatory pathways in multiple cell and tissue organs.13,19,20,31,93 GPS2/NR regulatory pathways were involved in cholesterol metabolism and transrepressive anti-inflammation related with farnesoid X receptor (FXR), small heterodimer partner (SHP), LXR and liver receptor homologue-1 (LRH-1),93-95 in human liver cell lines or primary hepatocyte-based in vitro studies. The in vivo study to investigate the liver function of GPS2 was recently published.24 In this study, albumin-cre was used to breed with GPS2 floxed mice to remove GPS2 in the mouse liver. The KO mice had enhanced feeding and fasting ketogenesis and reduced serum triglyceride.24 High throughput transcriptomic and cistromic analysis showed that GPS2 recruited mostly to PPRE motifs and regulated PPAR signaling pathways. GPS2 interacted with PPARα together with NCOR and stabilized the PPARα/NCOR complex and thereby inhibited PPARα activation in the mouse hepatocytes. More interestingly, in published genome-wide transcriptomic data in human NAFLD liver samples, GPS2 mRNA expression was positively correlated with NASH and fibrosis signature genes,96 further supporting the role of GPS2 to promote human NAFLD progression.

In contrast to the hepatocytes, GPS2 worked with SMRT to repress inflammation in both adipocytes and macrophages and thereby was negatively correlated with insulin resistance.
and T2D development in humans. The corepressor and transcription factor selectivity of GPS2 in different tissues remains to be solved.

1.5.2 GPS2 is an epigenomic coactivator and controls cholesterol efflux and lipolysis

Similar to TBL1 and TBLR1, the role of GPS2 as a coactivator was also reported. An earlier study in human liver cell line found that GPS2 interacted with histone demethylase Lysine-specific demethylase 4A (KDM4A) and histone acetyltransferases (HATs). This interaction was required for LXRα agonist-induced H3K9 demethylation and H3 acetylation at ATP-binding cassette sub-family G member 1 (ABCG1) locus, which activated the gene transcription in human hepatocytes and macrophages. GPS2 was also required for NFκB to mediate lipopolysaccharides (LPS) triggered ATP-binding cassette transporter A1 (ABCA1) expression in mouse and human macrophages. Similar mechanism was reported in adipocytes that GPS2/KDM4A worked as a pioneer complex to recruit PPARγ to the lipolysis genes such as adipose triacylglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) in mice. Noteworthy, around 30% of PPARα target genes are also downregulated in GPS2 KO mouse livers.

In conclusion, GPS2 not only worked as a corepressor to inhibit PPARα activity with the help of NCOR in the liver, but it was also required in transactivation pathways of some other TFs. How such opposite functions are controlled, for example in the posttranslational level, remains to be clarified.

2 CONCLUSIONS AND FUTURE PERSPECTIVES

In this review, we concluded current findings of the NCOR/SMRT corepressor complex in the PPARα signaling pathways and their physiological relevance in both mouse models and humans. PPARα is still among the most promising targets for treating liver metabolic disorders. Major efforts are required to further understand the molecular mechanisms (especially the coregulator networks) defining PPARα gene and tissue-selectivity in different signal and disease contexts for developing better and more-specific ligands. There are so far several challenges to achieve this goal.

2.1 The first challenge is to understand the physiology of different PPARα coregulators

Investigating the functionality of many coregulators in liver cells (both hepatocytes and immune cells) requires intensive phenotyping analysis using different tissue-specific KO models. It also has to be noted that the species difference of PPARα regulation exists. As a result, many of the findings in mice needs to be evaluated in humans as well. Therefore, it urges the development of more humanized mouse models.

2.2 The second challenge is to encrypt the genome-wide regulation code for those coregulators

Recent development of next generation sequencing (NGS) techniques allows genome-wide cistromic and transcriptomic analysis of coregulator networks. However, such analysis in coregulators remains difficult due to lack of solid antibodies and technical barriers in cistromic (ChIP-seq) procedures, as many of the coregulators require transcription factors to bind to the chromatin. More unbiased screening for functional PPARα interactomes in the chromatin level (using proteomic technologies) might also help to identify novel and specific coregulators.

2.3 The third question is to understand the switch on and off mechanisms of the coregulator complexes in response to different stimulus signals of PPARα

These involve the posttranslational modifications that stabilize or destroy the PPARα/coregulator complexes and the upstream kinases that contribute to such modifications. This could be important as kinases are more prominent pharmaceutical targets than coregulators. The interaction of different NR (such as PPARα/glucorticoid receptors, GRs) signaling in defining the ligand potent and specificity also represents a highly interesting and pharmaceutically important aspect.

There are also a group of questions regarding the PPARα/NCOR (SMRT) corepressor complexes. For example, what are the mechanisms of the selective interplay of NCOR but not SMRT with PPARα in the liver? How TBL1/TBLR1 co-activates PPARα and whether the process requires NCOR/SMRT complexes? What are the roles of the complex components in different metabolic (ie, triglycerides, cholesterol, glucose, amino acids, etc) pathways? All the questions requires further investigations.

Although directly targeting NCOR/SMRT complex remains difficult as the corepressors do not possess ligand binding domains. The developing protein and RNA technology might allow manipulation of the corepressor complexes in vivo in the near future. In addition, as the corepressor
expression themselves contributes to disease susceptibility and drug responses, future correlation analysis in different groups of patients (both polymorphisms and mRNA expression profiles) also helps to identify disease risk factor-associated traits.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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