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Review Article

Thyroid Hormone Receptor Coregulators in Metabolic Regulation

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Special Issue on

Role of Thyroid Hormone in Metabolic Homeostasis

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Abstract

It has been known for a long time that thyroid hormone regulates metabolism. Thyroid hormone action is primarily mediated by Thyroid Hormone Receptors (TRs). The transcriptional regulation by TRs is modulated by coregulators including coactivators and corepressors. Emerging evidence suggested that coregulators are critical for metabolic regulation mediated by TR. This review describes recent *in vivo* findings that improve our understanding of the roles of coregulators and provides an alternative way to enhance our knowledge on TR-mediated metabolic regulation. In order to delineate the complex mechanisms involved, we compare the results obtained from the researches employing different lines of mouse genetically modified. It is found that both corepressors and coactivators are indispensible for the full function of TR. We also discuss the challenge and future direction in the research field of thyroid hormone action in metabolism.

THYROID HORMONE AND THYROID HORMONE RECEPTOR

The active form of thyroid hormones (TH), 3,3'5-Triiodo-l-Thyronine (T3), play critical roles in growth, development, differentiation, and metabolism [1-5]. The circulating TH levels are tightly controlled by hypothalamic-pituitary-thyroid (HPT) axis, while the local TH levels are regulated by deiodinaseisozymes [6]. Many of the effects of TH are mediated by TH Receptors (TRs), which are ligand-inducible transcription factors that belong to nuclear receptor (NR) super family [4,7,8]. TH is able to positively regulate the expression of many target genes. In the absence of T3, TRs constitutively interact with Thyroid Response Element (TREs) in the promoter region of target genes and inhibit the basal transcription; in the presence of T3, T3 binds to TRs, resulting in conformation change of TR and transcriptional activation [4,8]. TH also inhibits gene expression in the presence of T3, the mechanisms of which is not well understood [9-11].

There are three major hormone binding TRs, TRβ1, TRβ2, and TRα1, which are encoded by two genes. Like other classical NRs, these major TR isoforms contain three major domains including A/B domain, DNA-Binding Domain (DBD), and Ligand-Binding Domain (LBD). A long-standing question in the research of TR is whether these isoforms have divergent functions. Targeted deletion or mutation of the TRα or TRβ genes in mice has shown that TR isoforms could play specific or overlapping roles depending on certain circumstances [12,13]. This complex way of regulation may be partly ascribed to the tissue-specific expression and/or receptor-specific activity of different TR isoforms [14]. Although it is well reckoned that different TR isoform exerts distinct function, the molecular mechanisms involved still remain to be elucidated.

TH-REGULATED GENES INVOLVED IN METABOLIC REGULATION

At transcription level, abundant key players involved in energy homeostasis, carbohydrate and lipid metabolism have been reported to be under the direct or indirect control of TH and TR. For instance, TR has been proved to positively regulate the expression of brown adipose tissue-specific Uncoupling Protein 1 (UCP1), ubiquitously expressed UCP2, and skeletal muscle enriched UCP3, which might explain one of the potent role of TR in the regulation of basal metabolic rate and energy expenditure [15]. Glucose transporter type 4 (GLUT4) and gluconeogenic Phosphoenolpyruvate Carboxy Kinase (PEPCK) expression are alsopositively regulated by TH, suggesting that TH increase glucose uptake and enhance glucose production in muscle and liver, respectively [16,17]. TR also regulates

mitochondrial glycerol-3-phosphatedehydrogenase gene (Gpd2), which is critical for glycerol production and serves as a major link between carbohydrate metabolism and lipid metabolism [18]. In liver, lipogenic genes such as Fatty Acid Synthase (FAS), Thyroid Hormone Responsive Spot 14 (THRSP), Malic Enzyme (ME), and acetyl-CoA-carboxylase (ACC) are positively regulated by TH, while pro-lipogenicstearoyl-CoA desaturase-1 (SCD1) is negatively regulated by TH [19-23]. In addition, hepatic carnitine palmitoyl transferase 1α (CPT1α), a rate-limiting enzyme for fatty-acyl-CoA transport and β-oxidation in the mitochondria, is a target gene positively regulated by TH [24]. Genes involved in cholesterol metabolism are also regulated by TRs such as, cholesterol 7a-hydroxylase (CYP7A), HMG-CoA Reductase (HMGCR), Low Density Lipoprotein Receptor (LDLR), and scavenger receptor class B member 1 (SR-B1) [25-27]. CYP7A controls cholesterol catabolism and bile acid synthesis. HMGCR determines the rate of cholesterol biosynthesis. LDLR and SR-B1 are involved in cholesterol uptake. It can be seen that genes involved in cholesterol synthesis and disposal are both controlled by TRs. The net effect of TH on cholesterol homeostasis might depend on the coordinated activity of these enzymes or receptors [27]. Adipose tissue metabolism is also well regulated by TRs. In addition to promote adipogenesis by regulating C/EBPα expression, TH increases lipolysis and the released fatty acid is delivered to liver and muscles for oxidation [4,8]. Collectively, TH and TR play pleiotropic roles in regulating metabolism and maintaining homeostasis.

NUCLEAR RECEPTOR COREGULATORS

The transcriptional activity of TRs is controlled through multiple ways. An NR coregulator, including coactivators and corepressors, has been shown to play important roles in modulating TR-mediated transcription [28]. These coregulators and the complexes consisting of them have undertaken roles including altering chromatin structure and contacting the basal transcription machinery [7,8]. Nuclear receptor corepressor (NCoR) and Silencing Mediator of Retinoid and Thyroid receptors (SMRT) are two of the well studied corepressors involved in TR function. NCoR and SMRT were described as prototypical NR corepressors [29]. TRs bind with NCoR with higher affinity than SMRT, and thus NCoR is believed to preferentially control transcription repression mediated by TR. In the absence of T3, NCoRor SMRT forms a complex with Histone Deacetylase 3 (HDAC3) and is recruited by TR to the promoter region of target genes to suppress transcription [30]. In the presence of T3, T3-bound TR disassociates corepressor complexes and recruits coactivator complexes with histone acetyl transferase activity to activate transcription [28,31]. Similar to that of TR isoforms, the activity of coregulators is spatially and temporally regulated, which coordinates with the regulation of TR isoform to achieve their selective functions [32-35]. Thus, the recruitment of different co-regulator complexes provides another layer in the transcriptional regulation by TH [35-38].

THYROID HORMONE RECEPTOR COREGULATORS AND METABOLISM

Emerging in vivo evidence suggests that NR coregulators are involved in diverse aspects of metabolic regulation. However, distinct coregulators might selectively bind to different NRs. Meanwhile, one target gene could be simultaneously controlled by multiple NRs. These innate complexities of regulation render us difficult to interpret the data obtained from individual genetic manipulated mouse model targeting the coregulator. Thus it is worthwhile to review the in vivo researches in recent days so as to help us better understanding the role of NCoR, SMRT, as well as other regulators on TR-regulated gene expression and metabolism, especially in the liver. We also apologize to all the researchers which have contributed to the field but are not cited here.

NCoR

NCoRi transgenic mice: The first in vivo evidence of the regulatory role of NCoR on TR-mediated transcription and metabolism was obtained from a transgenic mouse model with a variant form of NCoR (NCoRi) in the liver. Since NCoRi lacks the repression domains but retains the NR interaction domains, it has dominant negative activity on TR-mediated basal repression in a reporter assay [39]. To be noted, both endogenous NCoR and SMRT mRNA is increased in hypothyroid NCoRi transgenic mice, suggesting a compensatory responses. The expression of THRSP and another TR target gene, deiodinase 1 (DIO1), in hypothyroid NCoRi transgenic mice is significantly higher than that of wild type hypothyroid control mice, indicating that NCoRi is able to derepress basal repression in the absence of T3 (Table 1). In contrast, the expression of these two genes does not change in hyperthyroid NCoRi transgenic mice as compared with their hyperthyroid littermate controls, suggesting that NCoRi is not involved in transcriptional activation (Table 1). This result is in agreement with the concept that NCoR interacts with TR in the absence of T3 and is involved in TR-mediated basal repression. However, the effect of NCoRi on ME, another TR positively regulated gene, was not observed, suggesting that the action of NCoR on TR target genes is selective (Table 1). Thus, the in vivo data from NCoRi transgenic mice indicate that NCoRi selectively blocked basal repression of several TH positively regulated genes but not affected transcriptional activation [40]. Although the expression of lipogenic THRSP was altered in hypothyroid NCoRi transgenic mice, whether the expression of other lipogenic TR target genes, such as ACC, FAS, and SCD1, is also changed and whether these mice display dysregulation in hepatic lipid metabolism were not reported. As a result, we do not gain any further information on whether impaired NCoR function will consequently incur disturbed hepatic lipid homeostasis.

L-NCoRΔID mice: NCoR is recruited to NRs through an isoleucine rich motif termed a CoRNR box in its C-terminal Receptor Interacting Domains (RIDs) [41-43]. There three RIDs with different affinities in receptor binding [44-47]. TR has been shown to preferably bind NCoR in vitro via RID3, which is required for strong interactions with DNA-bound TR. Besides, RID3 must cooperate with RID2 to interact with a TR homodimer on DNA as each TR binds to one of the RIDs. Mice with a mutant NCoR without RID3 and RID2 (NCoRΔID) were developed to uncover the role of NCoR in TH-regulated biological processes [48].

Interestingly, the expression of TH target genes is differentially influenced in mice with a hepatic NCoRΔID (L-NCoRΔID)

	L-NCoRΔID	NCoRΔID	NCoRDADm	NCoRΔID +βPV	NCoRi	SRMT	SRC-1	SRC-1 +βPV
euthyroid								
TT4/TT3		De	N/De	De			In	
TSH		N	In	De		N	In	
TSHα		N	In			N		
TSHβ		N, De(βPV)	N	De		N	N	
FAS	In		In			In		
THRSP	In	In	In					
DIO1	In	N	N					
ME	In	N, In(βPV)		In		In		
CYP7A	In	N(In/NS), In(βPV)	N	In			N(De/NS)	N
HMGCR	In					In		
SCD1	In							
S-CH	N	N, In(βPV)		N		In	N(De/NS)	N
L-CH	N							
S-TG	N(In/NS)							
L-TG	N							
LW		In		In				
hypothyroid								
FAS	In		N					
THRSP	In	In	N(In/NS)		In		In	
DIO1	In	In	N		In		N	
ME	In	In			N		N	
CYP7A	In	N(In/NS)	In					
HMGCR	In							
SCD1	In							
S-CH	N	N(De/NS)				In		
L-CH	N							
S-TG	N							
L-TG	N							
hyperthyroid								
FAS	In		N(In/NS)					
THRSP	In	In	N(In/NS)		N		N	
DIO1	N	In	N		N		N	
ME	In	N(In/NS)			N		N	
CYP7A	In	N	N					
HMGCR	In							

Table 1 In, increase; De, decrease; N, no change; In/NS, increase but not significant; De/NS, decrease but not significant; (βPV), data from TRβPV study; +βPV, in TRβPV/PV mice; LW, liver weight; S-CH, serum cholesterol; L-CH, liver cholesterol; S-TG, serum triglyceride; L-TG, liver triglyceride

depending on TH status (Table 1). When L-NCoRΔID mice were rendered hypothyroid, the expression of genes positively regulated by TH (DIO1, GPD2, CYP7A, HMGCR) is derepressed (Table 1). This result indicates that NCoR plays a sufficient role in the basal repression of these genes by unliganded TR. In euthyroid state, the expression of these positively regulated TH target genes is elevated in L-NCoRΔID mice (Table 1). This is consistent with the notion that about half of the TRs are bound to TH in the euthyroid state. In addition, the expression of classic T3 targets (THRSP, FAS and ME) is significantly elevated in L-NCoRΔID mice in the hypothyroid state, which is unseen in control hypothyroid mice (Table 1). These data also indicate that NCoR plays a role in modulating T3 sensitivity. Surprisingly, the expression of those negatively regulated TH target genes is not altered in the liver of L-NCoRΔID mice in either hypothyroid or euthyroid state (not listed), suggesting NCoR plays limited role in negative regulation in the liver. Collectively, these important in vivo data clearly demonstrate that NCoR is TR corepressor and mediates unliganded TR action in basal repression for TH positively regulated gene [48].

The complexity of TR mediated transcription regulation is manifested by the hepatic cholesterol metabolism. As noted earlier, CYP7A is responsible for the cholesterol elimination. In hypothyroidism, unliganded TR suppresses the expression of CYP7A thus resulting in an elevated LDL cholesterol level. Theoretically, the significant derepression of CYP7A expression should have reduced total cholesterol level in hypothyroid or euthyroid L-NCoRΔID mice. Surprisingly, only a marginal decrease in LDL cholesterol level was observed. In addition, hepatic cholesterol content is unaltered. One of the reasonable explanations is that in both hypothyroid and euthyroid L-NCoRΔID mice the derepression of HMGCR and increased expression of other cholestrogenic genes might override the effect of enhanced CYP7A on cholesterol elimination.

Metabolically, THRSP, FAS, ME, as well as Gpd2 contribute to lipogenic process. However, the increased lipogenic gene expression in L-NCoRΔID mice does not lead to fatty liver and hypertriglyceridemia. This contradiction indicates that altered fatty acid disposal and/or TG elimination might be involved. Besides, whether L-NCoRΔID mice were defective in maintaining glucose homeostasis and whether PEPCK expression was altered were not clear. Therefore, whether NCoR is able to serve as a TR coregulator to interfere with glucose and lipid homeostasis through TH targets deserve more experimental evidence.

Liver X receptors (LXR) are ligand-activated nuclear receptors that can associate with NCoR [6]. TR and LXRs share a group of target genes in the regulation of lipogenesis and cholesterol metabolism. NCoRΔID lose the ability to bind with TR, but was still capable of binding with LXR although with a reduced ability. To figure out the outcome of this partly reserved binding ability with LXR, hepatocytes from L-NCoRΔID mice was employed to investigate the specific effect of NCoR on target genes for both TR and LXR. The expression of THRSP, DIO1 and SCD1 is increased in hepatocytes from L-NCoRΔID mice in the absence of LXR ligand. LXR ligand treatment, which dissociates NCoR form LXR, has no effect on DIO1, a target for TR but not LXR. LXR ligand also has no effect on THRSP, a common target for both TR and LXR. This result suggests that the repressive effect of NCoR on THRSP is TR specific. In contrast, the expression of SCD1, a positively regulated target of LXR, is increased by LXR ligand in hepatocytes either from L-NCoRΔID or control mice. These results suggest that the effect of NCoR on SCD1 expression is mediated by LXR but not TR.

NCoRΔID mice: The role of NCoR in TH signaling is also investigated by using NCoRΔID mice which express NCoRΔID globally [49]. The NCoRΔID mice showed reduced TH levels accompanied by unchanged Thyroid-Stimulating Hormone (TSH) level compared with control mice. The effect of NCoRΔID on the expression of TH positively regulated target genes (e.g. THRSP, DIO1, ME, Gpd2 and CYP7A) are very similar to that in the liver of either L-NCoRΔID mice and NCoRΔID mice regardless of thyroid status (Table 1). These results again suggest that disruption of NCoR and TR interaction increases TH sensitivity of peripheral tissues.

When NCoRΔID is introduced into TRβPV mice, a well characterized mouse model of Resistance to Thyroid Hormone (RTH), the expression of ME and CYP7A is derepressed compared with TRβPV mice [50,51]. Since TRβPV serves as an unliganded TR, it was postulated that the transcriptional regulation of TR target genes in TRβPV mice with NCoRΔID should be similar to that in either hypothyroid NCoRΔID mice or hypothyroid L-NCoRΔID mice (Figure 1). To be noted, the regulatory pattern of these hepatic TR target genes in NCoRΔID mice is comparable to hypothyroid $TR\beta^{-/-}$ mice, suggesting that TR mediates the repression of these target genes through NCoR (Figure 1).

Interestingly, after crossed with TRβPV mice, NCoRΔID mice displayed enlarged liver and increased total cholesterol. We speculated that the increased lipogenic gene expression might lead to enhanced lipogenesis and lipid storage, while increased cholesterol synthesis might attenuate the effect of CYP7A on cholesterol elimination. When compared homozygous TRβPV mice and NCoRΔID mice, in which the basal repression is absent, the liver was larger in homozygous TRβPV mice than that in NCoRΔID mice, suggesting that highly elevated TH levels in TRβPV/PV mice might result in abnormal fat mobilization. Additionally, NCoRΔID was able to increase the liver weight in homozygous TRβPV mice, further suggesting that NCoR acts through unliganded TR (Table 1 and Figure 1).

In summary, both L-NCoRΔID and NCoRΔID mice provide a unique model to assess the role of NCoR in TH action in vivo. The data obtained from these mice confirmed the critical role of NCoR in ligand-independent action of the TRs.

NCoRDADm mice: The role of NCoR in TH action has also been explored in NCoRDADm mouse in which the interaction of NCoR and HDAC3 is disrupted (Figure 1). HDAC3 is the main enzyme responsible for the repressive effect of NCoR [52]. The recruitment of HDAC3 is essential for TR mediated transcriptional repression [53,54]. Disruption of the NCoR–HDAC3 interaction in mice causes aberrant regulation of clock genes and results in abnormal circadian behavior [55].These mice are leaner and more insulin-sensitive owing to increased energy expenditure and altered β-oxidation cycling. In hypothyroid NCoRDADm mice, the expression of the hepatic CYP7A gene is derepressed.

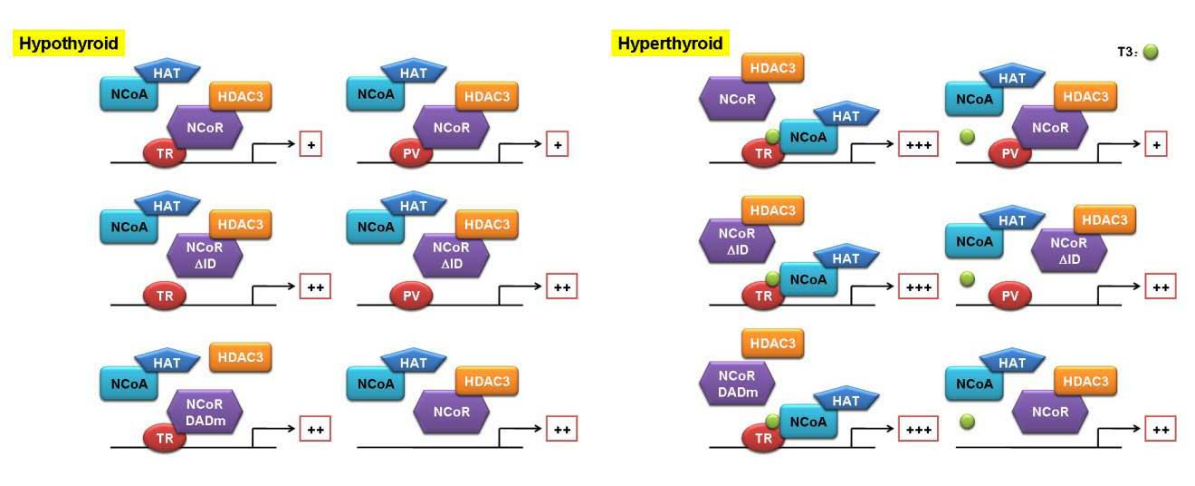

Figure 1 Schematic representation of the consequences of NCoR and NCoR mutant action on TR-mediated transcriptional regulation under different thyroid status.
In hypothyroidism (left panel), the absence of TH enable TR to interact with NCoR, which results in HDAC3 recruitment and basal transcriptional repression. NCoR mutant with either disrupted TR-interacting (NCoRΔID) or HDAC3-interacting (NCoRDADm) ability loses its repressive function on basal transcription. In hyperthyroidism (right panel), T3-bound TR disassociates NCoR complex and recruits coactivator (NCoA) complex containing enzymes with Histone Acetyltransferase (HAT) activity, which results in transcriptional activation. Since PV acts as an unliganded TR, NCoRΔID and NCoRDADm are able to derepress the transcription in the presence of PV regardless of thyroid status. In the presence of NCoRΔID, PV loses the dominant negative activity on transcriptional regulation, which leads to a phenotype similar to that seen in the absence of TR.

This derepressive effect by NCoRDADm disappears in either euthyroid or hyperthyroid states, suggesting that NCoR primarily functions in the absence of TH (Table 1). Euthyroid TH levels are sufficient to reverse the NCoR-dependent derepression of this gene. In addition, more abundant NCoR is found on the promoter of CYP7A as compared with SMRT. The expression of FAS and THRSP is significantly elevated or tended to be increased in the liver of NCoRDADm mice under different thyroid status. Surprisingly, DIO1 is unaffected regardless of thyroid status. Thus, the ability of the NCoR-HDAC3 interaction in regulating TH-responsive genes is gene dependent (Table 1). On the other hand, euthyroid NCoRDADm mice have higher TSH levels, which is associated with elevated TSHα expression in the pituitary. Thus, the NCoR interaction with HDAC3 is involved in both positively and negatively gene regulation by TH in vivo [56].

The difference between the NCoRDADm and L-NCoRΔID or NCoRΔID mice could be in part explained by the fact that in the NCoRDADm mice, the truncated NCoR can still be recruited to TR and thus block coactivator binding, which does not happen in L-NCoRΔID or NCoRΔID. Although altered lipogenic gene (FAS and THRSP) expression is observed, whether it would lead to any abnormality of lipid homeostasis in NCoRDADm mice requires further study.

It has been shown that T3 plays an important role in the regulation of hepatic autophagy, which is a critical step for the physiological mobilization and metabolism of fatty acids [57]. T3 is able to increase microtubule-associated protein 1A/1B-light chain 3 (LC3)-II levels, which is TR dependent. Moreover, knockdown of autophagy related 5 (ATG5) decreased T3-induced autophagy and β-oxidation, indicating that autophagy stimulated by T3 is necessary for the T3-mediated stimulation of fatty acid β-oxidation. To elucidate the role of NCoR in this process, NCoRDADm mice have been employed to examine the role of NCoR in TH-mediated autophagy. Interestingly, hypothyroid NCoRDADm mice do not display any repression of autophagy. LC3-II levels are higher in the hypothyroid NCoRDADm mice than in the wild-type littermates. This finding suggests that genes involved in autophagy normally repressed in hypothyroid wild-type mice may be derepressed in NCoRDADm mice. Although T3 is able to increase LC3-II levels in both NCoRDADm and wild-type mice, the LC3-II levels are lower in the NCoRDADm mice as compared with wild-type mice. Thus, NCoR is able to act as a corepressor of TR and modulates T3-mediated autophagy and lipid catabolism in liver [57].

NCoR and TRα regulated adipogenesis: The study of two strains of knock-in mutant mouse with either TRα1 (TRα1PV) or TRβ (TRβPV), two dominant negative mutant TRs, provided insightful ideas concerning the distinct role of TRα and TRβ [51,58]. Both TRα1PV and TRβPV completely lost T3-binding capacity and transcriptional activity. However, TRα1PV and TRβPV mice displayed distinct phenotypes in White Adipose Tissue (WAT) and liver [59,60]. WAT mass is reduced in TRα1PV mice, but not in TRβPV mice. TRβPV mice has fatty liver while the hepatic lipid content is low in TRα1PV mice. These observations indicate that TRα1 and TRβ1 mediate different aspects of T3 actions in lipid metabolism. TRα1PV inhibits adipogenesis through repressing the expression of peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα), two master regulators of adipogenesis, and their downstream adipogenic gene targets [59]. Interestingly, 3T3-L1 preadipocytes stably expressing equal amounts of TR1PV (L1-α1PV cells) or TRβ1PV (L1-β1PV cells) show different capacity of differentiation [61]. NCoR expression is decreased during adipogenesis.T3-stimulated adipogenesis is more severely impaired in L1-a1PV cells than in L1-β1PV cells, which was

associated with a stronger inhibition of the degradation of NCoR in L1-α1PV than in L1-β1PV cells [62]. NCoR is preferentially associated with TRα1PV and more resistant to degradation when associated with TRα1PV than with TRβ1PV. NCoR is more avidly recruited by TRα1PV than by TRβ1PV to the promoter of the C/EBPα [62].

To understand the role of NCoR in TRα1 regulated adipogenesis, NCoRΔID were introduced into TRα1PV mice [63]. NCoRΔID is neither able to interact wild type TRs nor PV mutant. Interestingly, NCoRΔID completely reversed the expression levels of PPARγ and C/EBPα in the WAT of $TR\alpha1^{PV/+}$, which re-activated the repressed adipogenic program. Moreover, NCoRΔID expression ameliorates many abnormalities in $TR\alpha1^{PV/+}$ mice. However, the mass of the adipose tissues were only partially corrected, suggesting that other transcription factors critical for adipogenesis that are not direct TR-target genes may indirectly contribute to the decreased size and mass of WAT.

Taken together, these findings suggested that different interaction of TR isoforms with NCoR, at least in part, underlies the TR isoform-dependent regulation of adipogenesis and lipid metabolism [62]. Since NCoR regulates the dominant negative actions of TRα1 mutant, NCoR could potentially serve as therapeutic targets for patients with mutations of the TRα gene. In addition, since the aberrant expression of NCoR could lead to severe lipidrelated disorders, NCoR could be considered as a potential therapeutic target in treating the abnormalities of lipid metabolism.

SMRTm RID Mice.

SMRT also interacts with TR through CoRNR motifs in their Receptor Interaction Domains (RIDs) [41-43,64]. The role of SMRT in TH action has been investigated in a mouse model with SMRT mutated in both RID1 and RID2 (SMRTm RID) [65]. This mutation disrupts the interaction between SMRT and TRs. SMRTm RID mice have normal serum cholesterol levels in euthyroid state. However, when rendered hypothyroid, hypercholesterolemia is significantly attenuated in SMRTm RID mice. The expression of LDLR, SR-B1, and HMGCR is significantly derepressed in hypothyroid SMRTm RID livers. Other TR target genes including lipogenic genes, FAS and ME, are derepressed. THRSP and CYP7A are tended to be up-regulated although it is not statistically significant (Table 1). These results suggest that SMRT mediates the TR effect on its positively regulated target genes in the liver. On the other hand, the negatively regulated pituitary TR target genes like TSHα and TSHβ, as well as serum TSH levels are not up-regulated in SMRTm RID mice regardless of thyroid hormone status (Table 1). This result indicates that the association of SMRT with TR is not required for ligand-induced negative regulation. SMRTm RID mice also display higher basal hepatic glucose production and exhibit insulin-resistant in muscle, which are features commonly seen in hyperthyroidism. These data indicate that the perturbed glucose homeostasis and metabolic defects in SMRTm RID mice might be due to the disruption of SMRT and TR interaction which results in abnormal TH signaling.

This finding together with those in NCoR mutant mice indicate that both NCoR and SMRT could act as TR corepressor in the regulation of hepatic metabolic homeostasis. The effect of NCoR or SMRT on lipogenesis and cholesterol metabolism might be similar. The distinct gene expression and lipid metabolism that observed in mouse models under different thyroid status might be ascribed to the specificity and potency of NCoR and SMRT on each individual target genes.

LCoR

LCoR (ligand-dependent corepressor) was originally identified as a corepressor of estrogen receptor α [66]. In contrast to the corepressors NCoR or SMRT, LCoR is associated with estrogen receptor α and some other nuclear receptors only in the presence of ligands through a single LXXLL motif, also referred to as a NR box. Further studies show that LCoR can interact with other transcription suppressors such as HDACs and CTBP [66-68]. Recently, LCoR was identified as a ligand-independent corepressor for TR [69]. The in vivo function of LCoR was explored in mouse liver. Ectopic expression of LCoR with adenoviral decreases the hepatic TG level in mice accompanied by downregulation of lipogenic genes (ACC, FAS, THRSP, ME) positively regulated by TR as well as non-lipogenic gene (DIO1). Interestingly, LCoR expression decreases in the livers of leptin-deficient (ob/ob) mice which show the feature of liver steatosis. Restoration the expression of LCoR in the liver of ob/ob mice ameliorates hepatic steatosis [69]. Further study revealed a shared binding surface of TRβ1 for LCoR and Steroid Receptor Coactivators (SRCs) in the presence of ligand, which results in competitive binding and reduces recruitment of SRC-1/3 to the promoter region of TR target genes when LCoR is present [69]. This study provides in vivo evidence that the TR-mediated hepatic lipid metabolism could be modulated by its corepressor LCoR; dysregulation of LCoR might be involved in pathogenesis of metabolic diseases. This study also provides a new target that could be aimed at for treating hepatic steatosis.

Other coregulators

Mice lacking TR coreguators, such as Steroid Receptor Coactivators (SRCs), receptor-interacting protein 140 (RIP140), and peroxisome Proliferator-Activated Receptor Gamma coactivator-1s (PGC-1s), have been extensively investigated to characterize their roles in metabolic regulation. However, only limited number of studies has linked the phenotypes of these mouse models to coregulator-mediated TR action.

SRCs are potent coactivator of transcription regulation. The SRC family consists of SRC-1, SRC-2 and SRC-3. SRC-1 deficient mice exhibit partial resistance to TH. However, TSHβ mRNA expression is not changed in the pituitary of SRC-1 knockout mice, suggesting that the effect of SRC-1 deficiency on TSH levels might be indirect [70] (Table 1). A marginal decrease in serum cholesterol level has been observed in SRC-1 knockout mice, although it is not significant. Hepatic CYP7A expression tends to be decreased in SRC-1 knockout mice, suggesting SRC-1 might be involved in TR-mediated CYP7A transcription [70] (Table 1). To be noted, when the issue is studied in TRβPV/PV mice, the effect of SRC-1 deficiency on either serum cholesterol level or CYP7A expression is abolished. This indicates that the role of SRC-1 on cholesterol metabolism is liganded-TR dependent [70] (Table 1). Since the data of other TR target genes involved in cholesterol uptake and biosynthesis are not available, the role of SRC-1 on

TR-mediated cholesterol metabolism requires further study. In addition, inactivation of SRC-1 does not affect the T3-dependent transcriptional activation of either DIO1 or ME, indicating that SRC-1 is not required for TR-mediated transcription of the two [71] (Table 1). In contrast, inactivation of the SRC-1 gene affected transcriptional regulation of the THRSP gene in liver. Down-regulation of THRSP mRNA in the absence of TH is completely abolished in the SRC-1 knockout mouse, suggesting that SRC-1 might affect THRSP expression in hypothyroid mice through mechanisms unrelated to TRs. T3 could not stimulate THRSP expression in hypothyroid SRC-1 knockout mice, indicating that SRC-1 is required for T3-mediated THRSP transcription [71].

Microarray analysis from the sample of mice deficient in SRC-1, SRC-2 or SRC-3 demonstrates that the three isoforms regulate distinct hepatic genes [72]. Most interestingly, the impact of SRC-2 gene ablation is an overall down-regulation of gene expression. SRC-2 deficiency leads to downregulation of many TR target genes, including Gpd2, FAS, HMGCR, and LDLR [72]. Since these genes are involved in gluconeogenesis, fatty acid synthesis and cholesterol synthesis/uptake, SRC-2 deficiency might cause defects in hepatic glucose and lipid homeostasis. This finding suggests that SRC-2 might regulate liver metabolism through controlling the transcription of these genes as a TR coactivator, although we cannot rule out the possibility that SRC-2 also acts as a coactivator of other transcriptional factor that also control the expression of these genes.

SUMMARY AND PROSPECTIVE

The studies we reviewed here suggest that TR action on target genes could be modulated in vivo by coregulators. Disrupting interactions between TRs and their repressors (NCoR and SMRT) enhances the sensitivity of TR to TH. Elevated LCoR expression blocks the recruitment of coactivator SRCs, thereby suppressing the transcription. Some of the works indicate that the regulation of TH on target genes in a particular tissue is dependent on the tissue-specific or time-specific expression of coregulators in addition to distinct TR isoforms, overall TH status, and local TH concentration.

Due to the potent roles, NR co-regulators could serve as novel targets in drug development to treating metabolic disorders. It is well known that vast majority of metabolic processes are regulated at transcriptional level through the dynamic recruitment of corepressors and coactivators to modulate chromatin and NR signaling. Enhancing NR function or increasing the sensitivity to endogenous ligand could be achieved through modulating coregulators. Targeting the corepressor–NR interaction should make it possible to modulate a specific pathway of interest. Since TH control metabolic pathways and function as a ligand of TR, TH analogues have been designed and tested as treatment especially for obesity, fatty liver, hypercholestroldemia and atherosclerosis. However, due to side effects, many drugs and prodrugs belongs to this class failed to enter large scale clinical application. Understanding the role of coregulators on TH action will provide more information, targets, and strategies to enhance TR function at right time and at certain location, and at safety dosage to treat a variety of metabolic diseases. Moreover, coregualtors themselves also could serve as potential therapeutic targets [73].

Although we learned a lot from the mouse models of coregulators, much information is still in need to turn the coregulators into readily practical targets for clinical treatment. More coregulator mutants like NCoRΔID which disrupt interaction selectively for TR are required, since current studies could not rule out the effect of coregulator mediated by NRs other than TRs. Rendering mice with coregulator mutant to hypothyriod and hyperthyroid will provide further information regarding the role of coregualtors on TH action. Alternatively, TR knockout, TRαPV and TRβPV mice are also very useful to investigate the role of coregulators in the absence of TR or in the presence of an unliganded TR. We have difficulty to compare the data from different mouse models to provide an overview of either gene expression or metabolic features because the studies were conducted within different TH status and not the same TR target genes were evaluated, neither did the metabolic parameters. Overexpression a coregulator into TR knockout mice might be an anther approach to distinguish its action through TR and other NRs. Finally, human genetic studies are required to further confirm the possible role of coregulaors in TH action, which is also helpful for drug development.

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