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Review Article

The Role of Corepressors in Thyroid Hormone-Regulated Metabolic Homeostasis

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Abstract

Thyroid hormone, acting through thyroid hormone receptors is a key regulator of metabolic homeostasis. Repression of transcription is critical component of thyroid hormone signaling and is mediated through the association of corepressor proteins with thyroid hormone receptors. In this review we will discuss recent results elucidating multiple roles for corepressors in mediating thyroid hormones regulation of metabolism.

Special Issue on
Role of Thyroid Hormone in Metabolic Homeostasis

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ABBREVIATIONS

TH: Thyroid Hormone; TR: Thyroid Hormone Receptor; TRE: Thyroid Response Elements; HPT: Hypothalamus-Pituitary-Thyroid Axis; NCoR: Nuclear CoRepressor; SMRT: Silencing Mediator of Retinoid and Thyroid-Hormone Receptors; RID: Receptor Interaction Domain; RTH: Resistance To Thyroid Hormone Syndrome; RAR: Retinoic Acid Receptor; TZD: Thiazolidinedione; HDAC: Histone Deacetylase; DAD: Deacetylase Activation Domain

INTRODUCTION

Thyroid Hormone (TH) is a central regulator of both basal metabolic rate as well as more specialized aspects of metabolic homeostasis such as lipid and glucose metabolism, a topic that will be extensively reviewed in other manuscripts in this issue. Thyroid Hormone Receptors (TRs) are high affinity receptors for TH and function as transcription factors that regulate transcription in response to TH levels. TRs are part of a larger family of transcription factors called the Nuclear Receptor (NR) superfamily that also includes receptors for vitamin D and vitamin A metabolites as well as receptors for other nutrient intermediates such as cholesterol and bile acids (reviewed in [1]. Vertebrates have two TR genes (TRα and TRβ) that are expressed as multiple isoforms (*e.g.* TRβ1 and TRβ2) [2-4]. Expression of TR isoforms is regulated in a developmental and tissue-specific manner, which is generally thought to reflect the biologically distinct yet somewhat overlapping functions of each receptor isoform.

TRs function to regulate gene transcription by binding directly to sequence-specific DNA elements, referred to as Thyroid Response Elements (TRE), and then either repressing or activating expression of regulated genes in a hormone dependent manner (reviewed in [5]). Genes regulated by TRs have been divided into two groups: positively regulated genes and negatively regulated genes. Positively regulated genes are repressed in the absence of TH and activated by TH binding to TRs. On the other hand, negatively regulated genes are active in the absence of TH and repressed in the presence of TH. Negative regulation of gene expression in response to circulating TH levels is critical to the negative feedback loop that regulates TH biosynthesis through the hypothalamus-pituitary-thyroid (HPT) axis. The molecular mechanism of negatively regulated genes is less well understood than positive regulation.

The mechanisms of positive regulation were described first at the molecular level. TRs activate and repress transcription through their interaction with corepressor and coactivator complexes. On positively regulated genes, in the absence of TH TRs preferentially interact with corepressor proteins. Upon binding TH, the TRs undergo a conformational change that causes the release of corepressors and allows the binding of coactivator proteins.

At the core of the corepressor protein complex are two homologous corepressor proteins, NCoR (Nuclear CoRepressor) and SMRT (Silencing Mediator of Retinoid and Thyroid-hormone receptors) [6-8]. NCoR and SMRT are high molecular weight proteins that function as a scaffold for the assembly of a large corepressor complex containing various proteins including the transducin-β-like homologs TBL1 and TBLR1, G protein pathway suppressor 2 (GPS2) and the histone deacetylase HDAC3, which function to repress transcription through interaction with and modification of the chromatin structure [9-11]. NCoR and SMRT share a conserved domain structure with the amino-terminal

region of the protein containing series of repression domains including interaction sites for the corepressor complex proteins. The carboxyl-terminus contains a series of Receptor Interaction Domains (RIDs) that are required for interaction with TRs and other NRs. Both NCoR and SMRT contain up to three RIDs (RID1-3), but the number and spacing of the RIDs is regulated by alternative mRNA splicing in both corepressors (Figure 1) [12-17]. The number and actual amino acid sequences of the individual RIDs dictate the affinity of the interaction between the SMRT and NCoR isoforms and specific nuclear receptors. For example, TRs preferentially interact with the N3 RIDs of NCoR and SMRT, whereas the Retinoic Acid Receptor (RAR) has a strong preference for the S2 RID of SMRT.

While NCoR and SMRT share a conserved structure and likely serve overlapping functions in some cellular contexts, it's clear from knockout mouse models of SMRT and NCoR that their functions are not redundant. NCoR knockout mice die at embryonic day 15.5 of defects in erythropoiesis and neuronal development, whereas SMRT knockout mice die at embryonic day 16.5 of cardiac development defects [18,19].

In working out the mechanisms of the roles of corepressor activity in TH signaling, deviations from the euthyroid state have been informative. Hyperthyroidism (or thyrotoxicosis) occurs when TH levels become abnormally elevated and is thought to be a condition where the negative feedback loops of the HPT axis in not functioning properly. Metabolically, patients with hyperthyroidism are lean and have a high basal metabolic rate and excellent cholesterol profiles. Unfortunately, hypothyroidism is toxic to the heart, resulting in life-threatening tachycardia and other arrhythmia. In hyperthyroidism, positively regulated genes are thought to be too activated and repression too diminished. Conversely, in hypothyroidism, low TH levels fail to active TH biosynthesis. Patients have reduced basal metabolism, weight gain, poor cold tolerance, and poor cholesterol profiles. Here positively regulated genes appear under activated.

Some people are born with autosomal dominant mutations in either TRβ (more common) or TRα (very few cases) gene. The resulting endocrine disorder is called Resistance to Thyroid Hormone (RTH) syndrome [20]. RTH syndrome causes patients to be refractory to thyroid hormone signaling, thus though patients have elevated circulating TH levels they appear to be either euthyroid or hypothryroid. In general, the mutations that cause RTH syndrome either cause TR to have a lower affinity for TH or impair the ability of TR to release corepressors in response to TH, and thus provide a unique window into how corepressors are involved in regulating thyroid hormone function [21,22].

THE ROLE OF COREPRESSORS IN REGULATING METABOLISM

Despite the confounding challenges posed by the embryonic lethality of both the SMRT and NCoR knockout mice, a series of targeted corepressor genetic manipulations in mice have clearly demonstrated a role for corepressors in controlling a variety of metabolic aspects.

Tissue-specific corepressor knockout mice

Recently three groups have described mice with tissue-specific ablations of NCoR and SMRT expression. The Adipose-Specific Knockout (AKO) of NCoR results in an increase in adipose tissue mass, likely due to increased adipocyte numbers due to an overall reduction in adipocyte size [23]. Despite this increase in adiposity, the NCoR AKO mice have improved glucose tolerance due to increased insulin sensitivity in liver, muscle, and fat. These metabolic effects were largely attributed to increases in PPARγ target-gene expression, effectively phenocopying treatment with the insulin-sensitizing Thiazolidinedione (TZD) class of drugs. The Muscle-Specific Knockout (MKO) of NCoR leads to mice with enhanced endurance due to increased muscle mass and mitochondria number [24]. This increase in oxidative metabolism in the NCoR MKO mice was largely attributed to increased ERR and PPARδ activity in these cells.

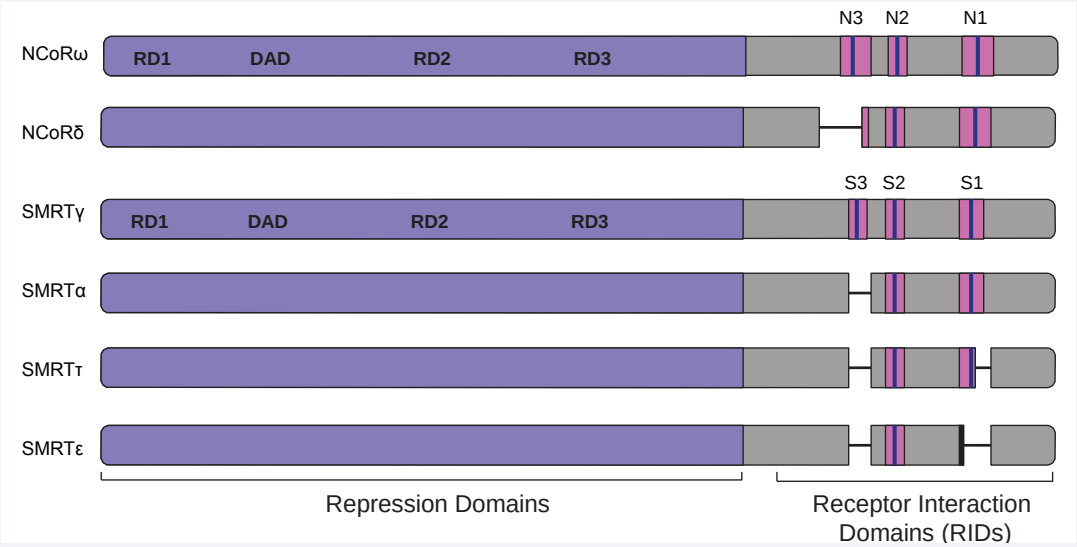

Figure 1 Schematic representation of alternatively spliced isoforms of SMRT and NCoR. The approximate location of Repression Domains (RD) and the Deacetylase Activation Domain (DAD) are indicated. Approximate locations of the individual Receptor Interaction Domains (RID, pink region with blue lines) are also indicated. Regions that are removed through alternative splicing are indicated with a horizontal line.

Finally ablation of NCoR expression in the liver (LKD) resulted in a dramatic increase in liver steatosis [25]. Paradoxically, the NCoR LKD mice have improved glucose tolerance, which is largely due to the diversion of intermediate metabolites from gluconeogenesis to lipid synthesis and storage. The phenotype of the NCoR LKD mice clearly resembles both the liver-specific ablation of HDAC3 and the orphan NR, Rev-erb. Ablation of SMRT expression in the liver, unlike NCoR, did not result in increased hepatic steatosis [25].

Corepressor mutant mice

Several targeted corepressor mutation knockin mice have also revealed roles for corepressors in regulating multiple aspects of metabolic homeostasis. Targeted mutations that disrupt either the S2 or both the S1 & S2 RID domains of SMRT demonstrate clear roles for SMRT in regulating adipose tissue function, glucose and lipid homeostasis and overall energy utilization [26,27].

Disruption of the SMRT RID domains results in dramatic weight gain and increased adipose tissue mass. These mice also have impaired glucose tolerance. Interestingly mutation of both the S1 & S2 RID domains results in a significantly lower energy utilization, indicating a role for SMRT mediating TR-regulated energy balance. Consistent with this, the increase in serum cholesterol that occurs when mice were made hypothyroid was significantly attenuated in the SMRT RID mutant mice, despite having similar changes in circulating TSH levels with PTU treatment.

NCoR and SMRT both bind and activate the histone deacetylase HDAC3 through a Deacetylase- Activating Domain (DAD) in the amino-terminal region of both corepressors [28]. Mutation of a single residue in the DAD of NCoR (Y478A) disrupts the interaction and activation of HDAC3 by NCoR [29]. These NCoR DADm mice are leaner and have improved insulin sensitivity due to increased energy expenditure [30]. They also have altered TH signaling, both centrally in the pituitary and in peripheral TH target tissues. The NCoR DADm mice have increased circulating TSH levels. A subset of positively regulated TR target genes in the liver are depressed.

Unexpectedly, the NCoR DADm mice also have enhanced expression of negatively regulated TR target genes including TSHα and DIO2 in the pituitary indicating a role for NCoR and HDAC3 in negative gene regulation by TRs. Together these observations demonstrate a role for the NCoR-HDAC3 corepressor complex in both central and peripheral TH signaling.

Finally, the targeted deletion of the region of NCoR containing the N3 and N2 RIDs (NCoRΔID), which are required for interaction with TR, have an altered TH "setpoint" [31,32]. The NCoRΔID mice have lower T_3 and T_4 levels but normal TSH levels, a condition that suggests central hypothyroidism (an HPT axis that does not respond appropriately to TH levels).

Paradoxically, these mice develop normally and have increased energy expenditure. Expression of several TR target genes is elevated (depressed) in the livers of NCoRΔID mice, especially under either induced hypothyroid or restored physiological TH_3 levels. Rather than having an increased sensitivity to TH, the HPT axis in these mice appears to have an altered euthyroid TH level and respond normally to acute changes in TH levels. Interestingly the thyroid gland of the NCoRΔID mice is more sensitive to TSH and has reduced unbound levels of T3 and T4 despite being normal in size.

That SMRT and NCoR interact with many nuclear receptors and other transcription factors confounds understanding the role they play in the control of metabolism via TRs. It is difficult to ascribe the metabolic perturbations observed in mice with TH signaling defects to be mediated by SMRT or NCoR acting specifically through TRs. For example, mice expressing NCoRΔID in the liver have improved cholesterol tolerance due to increased expression of bile acid metabolic enzymes like CYP27A1 and CYP3A11, genes whose expression is regulated by both TRβ1 and LXR [33]. By examining both the regulation of these genes in a LXRα deficient context and promoter occupancy by TR and NCoR, the authors were able to establish the role of NCoR-TRβ complex in the regulation of these genes.

The RTH mutations in TRs provide addition mechanistic insight into this process. Many of the mutations (most of which occur in TRβ) that are associated with RTH syndrome act as dominant negative mutations and result in forms of the TR protein that are impaired either in binding TH or that are impaired in their ability to release corepressors in response to TH [21,22]. Several mouse models of RTH have been created [34,35]. One of the best characterized of the RTH mutations is the "PV" mutation in TRβ (and subsequently introduced, synthetically, into TRα) that results from a frame shift mutation after P447, which replaces the carboxyl terminal fourteen residues with sixteen unrelated amino acids [36,37]. Knockin mice bearing the TRβ-PV mutation have enlarged livers owing to increased lipid accumulation within the liver [38].

Unlike mice with the TRβ-PV knockin mutation, the TRα-PV knockin mice have reduced adipose tissue mass owing to impaired adipogenesis [39]. The ability of both TR-PV mutations to impair adipogenesis, ex vivo requires NCoR [40]. Interestingly, adipogenesis involves a concomitant reduction in the amount of NCoR, which is also impaired to different extents by the TR-PV mutations.

A central role for corepressors in controlling TH signaling

The involvement of NCoR in the central regulation of TH signaling through TSH has been long been hypothesized and explored using ex vivo models [41,42]. Recently, NCoR's involvement in the central regulation of TH levels has been established using pituitary-specific expression of the NCoRΔID protein in mice [43]. The central role of corepressors in thyroid hormone resistance has also been established in vivo, by crossing the TRβ-PV and TRα-PV with the NCoRΔID mice [44,45].

Corepressors have generally been associated with transcriptional repression, hence their name. Recently, however, there is a growing appreciation for the role of corepressors in controlling gene activation as well. The first suggestions of this role *in vivo* came from the observation that SMRT ID mutations that blocked receptor interaction caused an increase in PPARγ target gene activation [27]. More recently, this has been

established for TRs as well [46]. Mice devoid of the coacitator Src-1 are reistant to thryoid hormone, presumably due to unopposed/inappropriate interaction with NCoR in the presence of TH [47]. This phenotype can be rescued by crossing the Src-1-/- with the NCoRΔID mice. In the absence of both NCoR and Src-1, the lower affinity interaction between TR and Src-2 is able to compensate for the loss of Src-1. These observations support a model where TH causes structural changes in TR that reduces the affinity for corepressors and increases the affinity for coactivators. In this model, the function of TH to shift the preference of TRs from cofactor complexes that repress transcription to ones that favor activation allows for corepressors to play a role in attenuating activation as well as mediating repression. This also means that the level of transcriptional response at a given hormone concentration is dictated by the relative expression levels of the various corepresors and coactivators, all of which have different affinities for TRs and other NRs.

Interestingly, the cell has likely recapitulated the SMRT and NCoR RID deletion experimental systems (at least in part). Vertebrate animals express an array of corepressor protein isoforms that differ in RID composition (Figure 1) [48-50]. Each of these corepressor isoforms differs in its affinity for TRs and other NRs, from the SMRTε isoform with only the S2 RID, which interacts with RAR with high affinity but has almost no measurable affinity for TRs, to isoforms of SMRT and NCoR with three RID domains that interact with TRs with relatively high affinity [51,52]. Cells naturally express isoforms of NCoR with either three RID domains (NCoRω) or only the N1 and N2 RIDs (NCoRδ). During adipogenesis, cells switch from expressing predominantly the NCoRω isoform to expressing the NCoRδ isoform in the mature adipocyte.

Ablating expression of the NCoRω isoform (leaving only the NCoRδ isoform) enhances adipogenesis in embryonic fibroblast cells isolated from mice lacking NCoRω.

Other Corepressors and TR

While SMRT and NCoR are the two most characterized and widely studied corepressors, a number of other corepressors have been identified (*e.g.* CoREST, Rip140, LCOR). Some of these are also likely to be involved in the regulation of metabolism by TRs. Ectopic overexpression of the Ligand-dependent CORepressor (LCOR) in the livers of ob/ob obese mice inhibited TRβ1 induced lipogenic gene expression, likely through decreased interaction between TRs and the Src coactivators [53].

Thyroid hormone serves as the primary regulator of both basal metabolic rate as well as more specific metabolite homeostasis. Corepressors are critical regulators of metabolic homeostasis, acting through many NRs. From the research presented here, it is clear that corepressors play key roles in both maintaining metabolic balance as well in controlling the feedback axis that regulates thyroid hormone levels thought their interaction with TRs. The concept that the levels and composition of the corepressor (and coactivator) repertoire in different cell types can control the both activation and repression by TRs is exciting and opens up new potential avenues to more selectively target TH actions in the treatment of thyroid disorders.

CONFLICT OF INTEREST

Neither MLG or BJM have any financial conflict of interest with the information presented in this manuscript.

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