Biochimica et Biophysica Acta 1830 (2013) 3876–3881

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

The *in vivo* role of nuclear receptor corepressors in thyroid hormone action ☆

Inna Astapova, Anthony N. Hollenberg *

Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215, USA

ARTICLE INFO

Article history:
Received 19 April 2012
Received in revised form 15 June 2012
Accepted 1 July 2012
Available online 16 July 2012

Keywords:
Thyroid hormone
Corepressor
T_3
Transcription

ABSTRACT

Background: The thyroid hormone receptor (TR) isoforms interact with a variety of coregulators depending upon the availability of T_3 to mediate their transcriptional effect. Classically, in the absence of ligand, the TRs recruit the nuclear corepressors, NCoR and SMRT, to mediate transcriptional repression on positively regulated TR target genes. However, new insight into the roles of NCoR and SMRT using *in vivo* models have better defined the role of nuclear corepressors both in the absence and presence of T_3.
Scope of review: This review will place the variety of *in vivo* nuclear corepressor mouse models developed to date in context of thyroid hormone action. Based on these models, we will also discuss how corepressor availability together with the levels of endogenous nuclear receptor ligands including T_3 controls multiple signaling pathways.
Major conclusions: Nuclear corepressors mediate repression of positive TR targets in the absence of T_3 *in vivo*. Even more importantly they attenuate activation of these targets at the normal physiological levels of ligands by TR and other nuclear receptors. While the role of corepressors in the regulation of negative TR targets and HPT axis remains poorly understood, lack of corepressor recruitment to TR in the animals leads to a compensatory change in the set point of HPT axis that allows to balance the increased sensitivity to T_3 action in other tissues.
General significance: Available data indicate that targeting specific interactions between corepressors and TR or other nuclear receptors presents a new therapeutic strategy for endocrine and metabolic disorders. This article is part of a Special Issue entitled Thyroid hormone signalling.

1. Introduction

With the cloning of the first thyroid hormone receptors in 1986 it soon became clear that the thyroid hormone receptors (TR) possessed the capability to silence transcription of target genes in the absence of thyroid hormone (TH) [1,2]. This action of the TRs is consistent with the detrimental clinical effects of hypothyroidism. Work by a number of laboratories determined that this silencing capability was mediated by the C-terminus of the TR via its interactions with unknown cellular protein(s) that were specifically recruited in transfection experiments [3]. The significance of this pathway was validated by the identification of highly homologous high molecular weight proteins that were able to interact with the C-terminus of the unliganded TR (and other nuclear receptors). These two proteins were both termed nuclear corepressors (CoRs) and named NCoR (nuclear receptor corepressor, NCoR1) and SMRT (silencing mediator of retinoid and thyroid hormone receptors, NCoR2). Both proteins (Fig. 1) share approximately 50% amino-acid identity and similar structural domains. The N-terminal portion of both NCoR and SMRT mediates transcriptional repression by recruiting a multiprotein complex through three separate repression domains [4–6]. Included in this complex is histone deacetylase 3 (HDAC3) whose enzymatic activity is activated by binding to CoRs and mediates chromatin remodeling and transcriptional repression [7,8]. Also, included in the complex is transducin binding protein like 1 (TBL1), its homolog TBLR1 and GPS2. Both TBL1 and TBLR1 bind to histones and appear to be involved in transcriptional activation and the clearance of the CoR complex while the role of GPS2 remains less clear though it is likely structurally required for maintenance of the CoR complex [9,10].

In contrast to the N-terminus of the NCoR and SMRT, the C-terminus mediates interactions between the CoRs and the TR and other nuclear receptors (NR). Both NCoR and SMRT have exons that encode 3 separate receptor interacting domains (RIDs) that contain a core isoleucine rich motif that is essential for NR-binding [11–13]. However, because of alternative splicing not all RIDs are expressed in all tissues. Interestingly, the most N-terminal of the RIDs (N3 in NCoR and S3 in SMRT) binds the TR with high avidity, while N2 also prefers the TR especially when compared to S2, which prefers the

☆ This article is part of a Special Issue entitled Thyroid hormone signalling.
* Corresponding author. Tel.: +1 617 735 3268.
E-mail address: thollenb@bidmc.harvard.edu (A.N. Hollenberg).

0304-4165/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbagen.2012.07.001

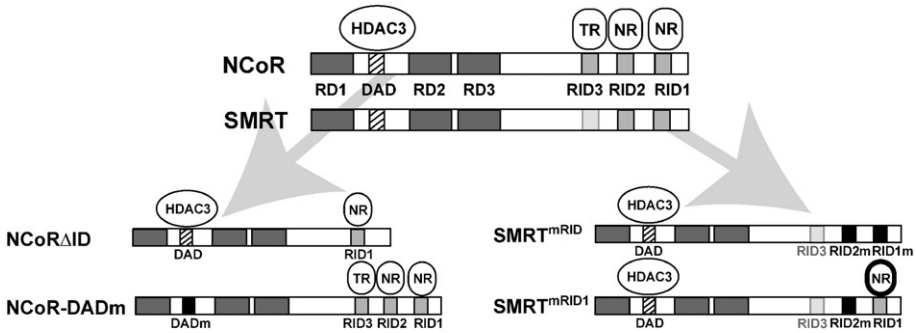

Fig. 1. Schematic representation of the structure of wild type NCoR and SMRT as well as various mutants discussed in this review. Repression domains (RD), deacetylase activation domain (DAD) and receptor-interacting domains (RID) are indicated. RID3 of SMRT is shown in lighter color to reflect the fact that the predominantly expressed SMRT isoform contains only RID2 and RID1.

retinoic acid receptor (RAR) [14–17]. Because of the different preferences of the RIDs for the TR it remains possible that NCoR and SMRT have non-redundant roles in the regulation of thyroid hormone action *in vivo*.

While NCoR and SMRT are felt to mediate the repressive functions of the unliganded TR or mutated TRs found in the syndrome of Resistance to Thyroid Hormone (RTH), it is also clear that the unliganded TR activates genes that are negatively regulated by TH. This feature suggests that the corepressors may have paradoxical activating functions on certain target genes. While cell culture studies have attempted to discern the role of both NCoR and SMRT in TH action, they have been complicated by the fact that many cell lines fail to express functional TR isoforms and TR responsive genes. Thus, the real role of NCoR and SMRT in TH-action is best discerned using mouse genetic models and the remainder of this review will focus on the advances made using an *in vivo* approach.

2. NCoR and SMRT knockout models

The first attempts to elucidate *in vivo* roles of co-repressors revealed the complexity of their physiologic functions beyond NR signaling. In 2000 the first global NCoR knock-out mouse was generated [18]. NCoR$^{-/-}$ animals exhibited defects in definitive erythropoesis and thymocyte and neuronal differentiation by embryonic day (E) 13.5. Furthermore the knockout of NCoR led to embryonic lethality by E15.5. However cultured mouse embryonic fibroblasts (MEFs) obtained from NCoR$^{-/-}$ embryos demonstrated the role of NCoR in the ligand-independent repression by RAR and TR, as well as an antagonist-bound estrogen receptor (ER). Interestingly, NCoR$^{-/-}$ embryonic livers showed increased expression of carbonic anhydrase II, a known positive TR target, thus confirming the importance of NCoR for TR-mediated repression in the absence of TH.

Subsequently, a SMRT knock-out was also developed and shown to lead to embryonic lethality [19]. SMRT$^{-/-}$ animals die before E16.5 because of a defect in heart development, namely a hypoplastic ventricular wall and a defect in ventricular septation. This defect is due to a disruption of a specific interaction between SMRT and a forkhead protein, FOXP1 [20]. When the lethality was overcome by myocyte-specific expression of SMRT, the development of SMRT$^{-/-}$ animals also revealed a critical role for SMRT in forebrain development and maintenance of the neural stem cell state through its interactions with RAR and Notch signaling, but no observations as to the role of SMRT in TR signaling were made.

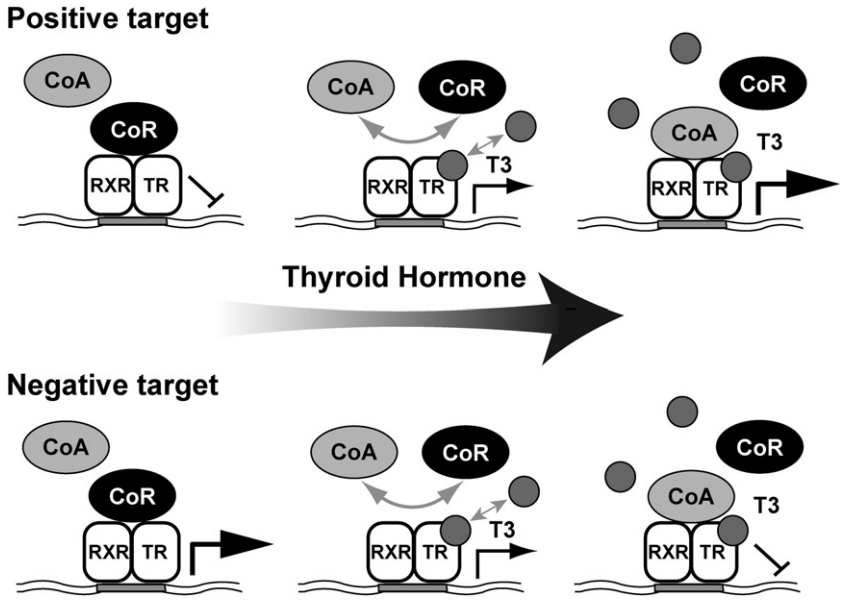

Fig. 2. A model of TR-mediated regulation of transcription. On a positively regulated target gene, in the absence of thyroid hormone (upper left) TR-RXR hederodimer recruits the corepressor complex to repress transcription. In the presence of high concentrations of TH (upper right) most of the receptors bind TH which induces the conformational change that leads to the release of corepressors and recruitment of coactivators to maximally activate transcription. At intermediate concentrations of TH corresponding to a normal euthyroid state (upper middle) only some of the receptors bind the ligand. The complex between TR, hormone, coactivators and corepressors is in a dynamic balance that achieves moderate activation of transcription. Removal of corepressors at this state results to the increased availability of TR for the ligand and coactivators, leading to the increased sensitivity to the hormone. Paradoxically, on negatively regulated targets, corepressor complexes recruited in the absence of hormone may activate transcription, while coactivators that are recruited when TR binds TH mediate transcriptional repression.