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REVIEW

Crosstalk of thyroid hormone receptor and liver X receptor in lipid metabolism and beyond

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Abstract. Thyroid hormone receptors (TRs) and liver X receptors (LXRs) are members of the nuclear receptor superfamily. Although LXRs and TRs belong to two distinct receptor subgroups with respect to ligand-binding affinity, the two receptor systems show similarity with respect to molecular mechanism, target genes, and physiological roles. Since both TRs and LXRs play an important role in metabolic regulation, form heterodimers with retinoid X receptors (RXRs), and bind to direct repeat-4 (DR-4) with identical geometry and polarity, crosstalk between these two receptors has been reported, especially on lipid metabolism-related genes. Recently, several types of crosstalk between TRs and LXRs have been identified and crosstalk has also been observed in other physiological systems such as central nervous system rather than lipid metabolism. In this review, recent advances in elucidating the molecular mechanisms of the crosstalk between these two nuclear receptors are discussed, with the aim of finding a perspective on unknown roles of TRs and LXRs.

Key words: Thyroid hormone, Thyroid hormone receptor, Liver X receptor, Crosstalk

1 Thyroid hormone and thyroid hormone receptors

Thyroid hormone is a key regulator controlling human metabolism and has great impact on lipid homeostasis in particular [1-3]. In fact, thyroid hormone status could cause drastic metabolic changes in humans. For instance, hypercholesterolemia is well characterized by hypothyroidism in either an overt or a subclinical state [1-3]. On the other hand, thyrotoxic patients with Graves' disease demonstrate hypermetabolism associated with reduced cholesterol levels in blood [1-3]. In fact, the role of thyroid hormone and thyroid hormone receptors (TRs) in the regulation of cholesterol metabolism has been examined intensively [1, 3, 4]. However, it still remains unclear how thyroid hormone affects triglyceride metabolism [5-9].

Thyroid hormone consists of thyroxine (T4) as a precursor of triiodothyronine (T3), which is an active form of the hormone [10]. TRs are nuclear hormone receptors, to which T3 binds at a high-affinity order as a native ligand. TRs possess at least two isoforms, TR-α and -β (Nr1a1 and Nr1a2), and several isoforms exist as two or three subtypes, respectively (α-1, α-2, β-1, β-2, and β-3) [11, 12]. TR-α1 is widely expressed in tissues including heart, muscle, intestine, bone, and brain and plays a key role in regulating postnatal development and cardiac metabolism, whereas TR-β regulates multiple steps in hepatic metabolism as well as thyroid hormone levels [12].

2 Liver X receptors

The liver X receptors (LXRs) also belong to the nuclear receptor family that plays pivotal roles in the transcriptional control of lipid and carbohydrate metabolism

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Abbreviations: thyroid hormone receptor (TR), liver X receptor (LXR), retinoid X receptor (RXR), direct repeat-4 (DR-4), thyroxine (T4), triiodothyronine (T3), T3 response element (TRE), LXR responsive element (LXRE), acetyl-CoA carboxylase (ACC), cholesterol 7-alpha-hydroxylase (CYP7A1), electromobility shift analysis (EMSA), ATP-binding cassette transporter A1 (ABCA1), high-density lipoprotein (HDL), sterol response element-binding protein (SREBP), chromatin immunoprecipitation (ChIP), carbohydrate response element-binding protein (ChREBP), type 1 deiodinase (DIO1), type 2 deiodinase (DIO2), nuclear receptor corepressor (NCoR), silencing mediator of retinoic acid and thyroid hormone receptor (SMRT)

[13, 14]. In addition to their function in lipid homeostasis, LXRs act to modulate immune and inflammatory responses in macrophages [15]. LXR exists as two isoforms, LXR-α and -β (also referred to as Nr1h3 and Nr1h2, respectively) [16, 17]. LXR-α is highly expressed in the liver, and is expressed at lower levels in the adrenal glands, intestine, adipose tissue, macrophages, lung, and kidney, whereas LXR-β is ubiquitously expressed in general tissues [18]. Although TRs and LXRs belong to distinct receptor subgroups with respect to ligand-binding affinity [19], the two receptor systems show similarities with respect to molecular mechanisms, target genes, and physiological roles [19, 20].

Both TRs and LXRs form heterodimers with RXR, and bind to TR and LXR responsive elements (TREs and LXREs), respectively, which consist of direct repeats (DRs) of the core sequence AGGTCA separated by four nucleotides (DR-4) [16, 17, 21, 22] with identical geometry and polarity [19, 20, 23, 24]. Furthermore, the fact that a large proportion of thyroid hormone-targeted genes are regulated simultaneously by LXR supports the hypothesis that there is physiological crosstalk of TR-LXR [20, 25]. In recent years, on the basis of these similarities of receptors, crosstalk between the two receptors on the target gene promoters has been reported by some groups including our own. In this review, the TR-LXR crosstalk is classified into several types with the aim of providing an overview of this crosstalk, especially in the field of lipid metabolism, in addition to the crosstalk in other fields such as neurodegenerative disorders.

1) Crosstalk by competitive binding to a DNA site (Fig. 1)

Acetyl-CoA carboxylase-α (ACC-α)

Acetyl-CoA carboxylase (ACC) is one of the enzymes that convert excessive dietary carbohydrate into triacylglycerols. ACC catalyzes the ATP-dependent carboxylation of acetyl-CoA to yield malonyl-CoA, which is the donor of all but two (ω) of the carbon atoms for the synthesis of long-chain fatty acids. This reaction is the pace-setting step of the fatty acid synthesis pathway [26, 27]. Zhang *et al*. identified that heterodimers of both RXR/TR and RXR/LXR bind to T3 response element (TRE) in chicken ACC-α gene promoter and that these heterodimers mediate the stimulation of ACC-α expression caused by T3 [28].

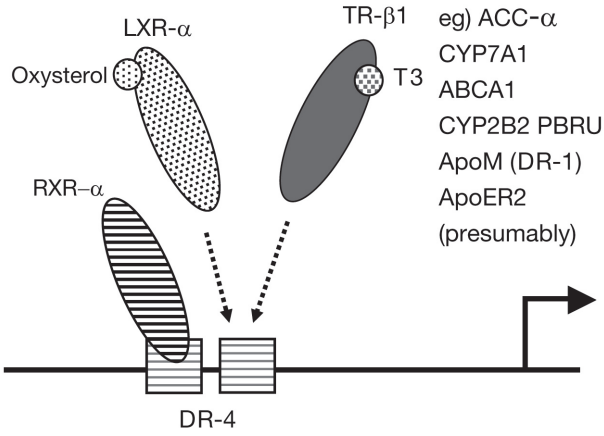

Fig. 1 Crosstalk by competitive binding to a DNA site
Since TRs and LXRs share the same DNA binding site, DR-4, competitive binding to DR-4 in several gene promoters has been reported.

Cholesterol 7-alpha-hydroxylase (CYP7A1)

Cholesterol 7-alpha-hydroxylase (CYP7A1) is a rate-limiting enzyme for cholesterol excretion by the conversion of cholesterol to bile acids [29] and is one of the genes that have been most intensively examined for crosstalk between TR and LXR. Gullberg *et al.* showed that the T3-induced stimulation in CYP7A1 activity and its mRNA level is lost in TR-β knockout (-/-) mice but not in TR-α1-/-mice, indicating that TR-β mediates T3 action on CYP7A1 activity and that TR-β, consequently, functions as a major regulator of cholesterol metabolism *in vivo*. However, dietary cholesterol can induce CYP7A1 expression and activity in T3-deficient TR-β -/- mice and these animals do not develop hypercholesterolemia to the same extent as do wild-type (WT) controls [30]. Since LXR-α has been proposed to be an important factor in regulating CYP7A1 activity in response to dietary cholesterol [31, 32], cholesterol feeding is hypothesized to activate LXR-α to induce CYP7A1 expression in TR-β-/- mice.

Our group established a TR-β mutant mouse as an animal model for resistance to thyroid hormone, which harbors the TR-β Δ337T mutation introduced by homologous recombination (TR-β knock-in (KI) mouse) [33]. In the hypothyroid state, a high-cholesterol diet increases serum cholesterol level in WT animals, but the same diet either does not affect or reduces its level in mutant homozygous (MUT) mice. A high-cholesterol diet markedly induces CYP7A1 levels in MUT but not WT mice in the hypothyroid state. The observations of elevation of CYP7A1 mRNA levels followed by reduced hepatic cholesterol content in

MUT animals are likely to indicate significant crosstalk between TR-β and LXR-α, which both bind to a DR+4 element in the CYP7A1 promoter. In transient transfection studies, WT TR-β antagonizes LXR-α-induced activation of CYP7A1 promoter; however, this action is lost in MUT TR-β. Electromobility shift analysis (EMSA) revealed that LXR/RXR heterodimers bound to the DR+4 element in the presence of MUT TR-β but not WT TR-β. Thus, in TR-β mutant animals, LXR/RXR heterodimer formation is dominant on the DR-4 site in mouse CYP7A1 promoter and induces the promoter activity upon dietary cholesterol administration. This is the first report to demonstrate crosstalk between TR-β and LXR-α *in vivo* [34].

As mentioned above, both TR-β and LXR-α regulate the activity of mouse CYP7A1 gene promoter [35-41]. However, LXR does not affect the activity of rabbit [42] or human [43] CYP7A1 gene promoter, whereas TR-β regulates both rodent and human CYP7A1 gene promoter activity [44], suggesting that there is a species difference in the TR-LXR crosstalk. This is due, at least in part, to the existence or absence of LXR response element (LXRE); a functional LXRE is present in rodent but not in human CYP7A1 gene promoter [39].

ATP-binding cassette transporter A1 (ABCA1)

The ATP-binding cassette transporter A1 (ABCA1) is involved in the regulation of cholesterol efflux from cells. Mutations in ABCA1 give rise to familial high-density-lipoprotein (HDL) deficiency and Tangier disease with extremely low levels of plasma HDL [45]. Both RXR-α/TR-β and RXR-α/LXR-α heterodimers can bind to the DR-4 element of the ABCA1 gene promoter [46]. TR-β together with its ligand, T3, suppresses ABCA1 transcriptional activity, even in the presence of LXR-activating oxysterols. Heterodimers of RXR-α/TR-β and RXR-α/LXR-α respectively suppress and activate ABCA1 transcription in the cell culture system. These data indicate that LXR-α and TR-β exert their reciprocal crosstalk on ABCA1 gene promoter at the transcriptional level.

CYP2B2 phenobarbital response unit

Hepatic CYPs (cytochrome P450s) play a critical role in regulating the metabolism of hydrophobic xenobiotics and endogenous hydrophobic metabolites [47]. The genes encoding these enzymes are either expressed constitutively or induced by various chemicals [48]. For instance, PB (phenobarbital) leads to the induction of the rat CYP2B2 gene [49]. A 163 bp enhancer in the CYP2B2 5' flanking region constitutes a PBRU (PB response unit) and confers PB inducibility. The PBRU contains several binding sites for transcription factors. In fact, each of NR1, NR2, and NR3 possesses DR-4s [50]. RXR/TR and RXR/LXR heterodimers bind to NR3, suggesting crosstalk of these two nuclear receptors in a competitive manner for NR3.

Apolipoprotein M

Apolipoprotein M (apoM) plays an important role in the biogenesis and the metabolism of anti-atherogenic HDL particles in plasma and is expressed primarily in the liver and kidney. RXR/TR and RXR/LXR heterodimers bind to a hormone-response element (HRE), which consists of DR-1 at -33 to -21 bp in human apoM gene promoter. Both T3 and 22(R)-OH-cholesterol induce this gene promoter activity [51]. It is of note that the HRE constitutes DR-1, but not DR-4, which is not typical for the competitive binding of the two receptors of TR and LXR.

Apolipoprotein E receptor 2 (ApoER2)

Apolipoprotein E receptor 2 (ApoER2) and its ligand reelin are essential for the migration of developing cortical neurons and their localization to their correct layer of the cortex [52, 53]. Cortical abnormalities observed in LXR-β -/- mice are strikingly similar to defects produced by mutations of apolipoprotein E receptor 2 (ApoER2) [54]. In LXR-β -/- mice, ApoER2 gene expression, which is positively regulated by LXR-β and TR-α, is reduced at the later embryonic stage. However, at the postnatal stage, this gene expression is much higher than that in WT controls. This suggests that thyroid hormone and TR-α would compensate ApoER2 gene expression in LXR-β -/- mice [53], indicating that crosstalk of the two receptors exists in the central nervous system.

2) Crosstalk in a DR-4 binding-independent manner

Sterol response element-binding protein (SREBP)-1c

Sterol response element-binding protein (SREBP)-1c is a key regulator of fatty acid metabolism and plays a pivotal role in the transcriptional regulation of different lipogenic genes to mediate lipid synthesis [55-57]. The type of TR-LXR crosstalk is complicated for this

gene promoter. LXRs bind to an LXR-binding site in the SREBP-1c promoter and activate SREBP-1c transcription in the presence of LXR agonists such as oxysterol [58, 59].

The mouse SREBP-1c promoter contains two DR-4 sites (LXREs) and LXRs stimulate promoter activity through binding to the sites. Since LXRs and TRs share the DR-4 site, we first speculated that TRs would also regulate the mouse SREBP-1c promoter through binding to the DR-4 site. In fact, our EMSA data clearly showed that the RXR-TR heterodimer binds to both the DR-4 site and LXRE. Kawai *et al*. constructed LXRE-thymidine kinase proximal promoter luciferase plasmid for their luciferase assays and showed that the heterologous promoter is up-regulated by both T3 and LXR agonist through RXR/TR and RXR/LXR heterodimer binding to the DR-4 sites [60]. On the heterologous promoter, TR-β functionally interferes with transactivation by LXR-α, whereas LXRs do not deteriorate promoter induction by TR-β, suggesting that RXR/TR heterodimer predominantly binds to the LXREs. These data suggest that TR and LXR competitively bind to canonical LXRE. However, *in vivo*, SREBP-1c gene expression is negatively regulated by thyroid hormone [61]. Moreover, native mouse SREBP-1c promoter activity is down-regulated by TR. Site 2 (GCCTGACAGGTGAAATCGGC) located around the transcriptional start site in mouse SREBP-1c gene promoter is responsible for the negative regulation by T3. EMSAs showed that RXR/TR but not RXR/LXR binds to Site 2. *In vivo* chromatin immunoprecipitation (ChIP) assay demonstrated that T3 induces recruitment of TR-β, but not LXR-α, to Site 2. Human SREBP-1c gene promoter is also negatively regulated by thyroid hormone [61]. These data indicate that, even though both TR and LXR competitively bind to the DR-4 site on the gene promoter, LXR positively regulates the gene expression. Additionally, the antagonism is shown to affect the gene regulation by thyroid hormone. Thus, mouse SREBP-1c gene promoter activity is regulated by TR-β in a DR-4-independent manner (Fig. 2A). This could be another type of TR-LXR crosstalk.

LXR-α

Human LXR-α autoregulates its own gene promoter through binding to the LXREs [62-64]. Thyroid hormone up-regulates mRNA expression of mouse LXR-α, but not LXR-β, in the liver, but cholesterol administration does not affect the LXR-α mRNA levels [65]. The human LXR-α gene promoter contains three cognitive LXREs, whereas neither half-sites of TREs nor those of LXREs are found in the mouse [24]. Although the positive TRE is located between -1300 bp and -1240 bp in the mouse promoter, where TR or LXR does not bind directly to Site A, TR-β is recruited to Site A, suggesting the presence of a protein complexed to intermediate TR-β to Site A [65] (Fig. 2B). This is one of the crosstalks; LXR-α gene expression itself is regulated by TR-β.

3) Crosstalk preferring DR-4 binding

Carbohydrate response element-binding protein (ChREBP)

Carbohydrate response element-binding protein (ChREBP) as well as SREBP-1c plays a pivotal role in the generation of hepatic lipogenesis in response to changes in glucose in the liver [66-68]. We have demonstrated that ChREBP gene expression is positively regulated by thyroid hormone [69]. The region of mouse ChREBP gene promoter contains two DR-4 sites (LXRE1 and LXRE2) and EMSAs demonstrated that LXR-α and TR-β1 differently bind to these elements: LXR-α binds to LXRE1 and TR-β1 binds to LXRE2. These observations suggest that TR and LXR preferentially bind to DR-4 sites. Human ChREBP gene expression and its promoter activity are also up-regulated by thyroid hormone.

Another group produced data to support our conclusion that TR and LXR recognize different response elements on the ChREBP promoter and that there is crosstalk between LXR and TR signaling on the ChREBP promoter in the liver. This is not the case in white adipose tissue, where LXR does not regulate ChREBP expression [70] (Fig. 3).

4) Crosstalk *via* thyroid hormone metabolism

LXR affects thyroid hormone metabolism by regulating type 2 deiodinase

Type 2 deiodinase (DIO2) promotes the local conversion of T4 to form T3 in thyroid hormone target tissues [10]. Administration of an LXR agonist reduces the T3/T4 ratio in plasma associated with decreased expression of type 1 deiodinase (DIO1) in the liver and DIO2 mRNA in the thyroid gland [71]. LXR-α/β knockout mice exhibit ectopic liver expression of DIO2, which is activated by thyroid hormone and regulates the function

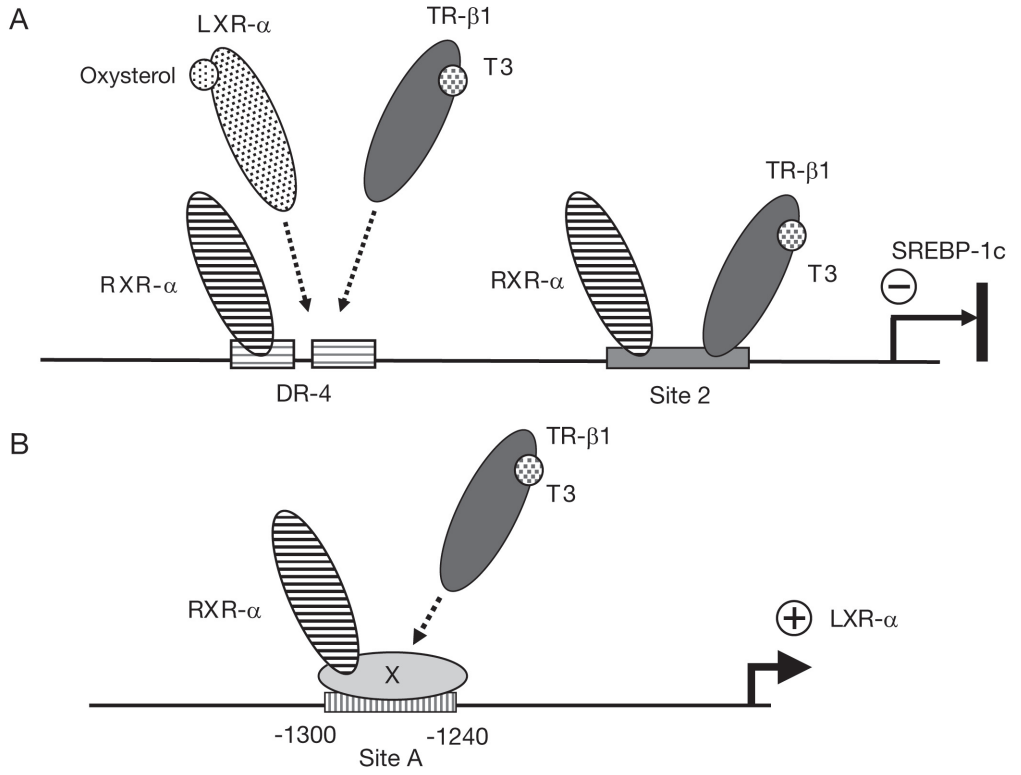

Fig. 2 Crosstalk in a DR-4 binding-independent manner
X: interacting protein (unknown)

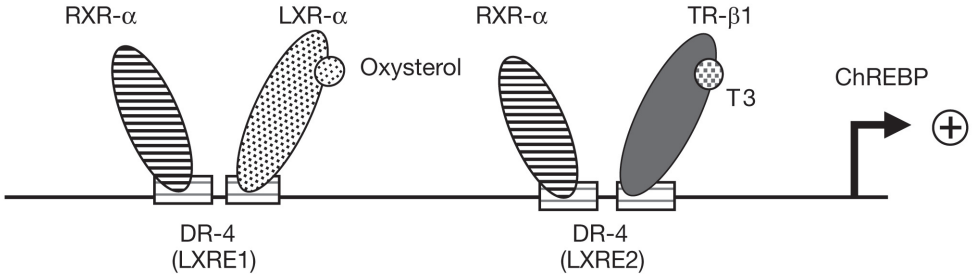

Fig. 3 Crosstalk demonstrating a DR-4 preference to bind
The distance between LXRE1 and LXRE2 is only 8 bp in mouse ChREBP gene promoter.

of thyroid hormone by converting T4 to T3 [72] (Fig. 4). Administration of 22(R)-OH-cholesterol, an LXR agonist, and 9-cis retinoic acid (9-cis RA), a ligand for the heterodimeric partner of TR and LXR, RXR, negatively regulate the activity of human DIO2 (hDIO2) gene promoter. *In vivo*, cholesterol/9-cis RA inhibits DIO2 activity that mediates T3 production [73]. This is another type of TR-LXR crosstalk by which LXRs regulate the metabolism of thyroid hormone.

5) Crosstalk *via* squelching of co-repressors

Nuclear receptor corepressor (NCoR), silencing mediator of retinoic acid, and thyroid hormone receptor (SMRT) corepressors [74, 75] are required for the negative response mediated by LXR in macrophages [76]. In the liver, a mutant NCoR protein (L-NCoRDeltaID mice) cannot interact with the TR [77]. NCoR recruitment to LXR is also impaired in mice carrying this mutant NCoR. Thus, both TR and LXR bind to core-

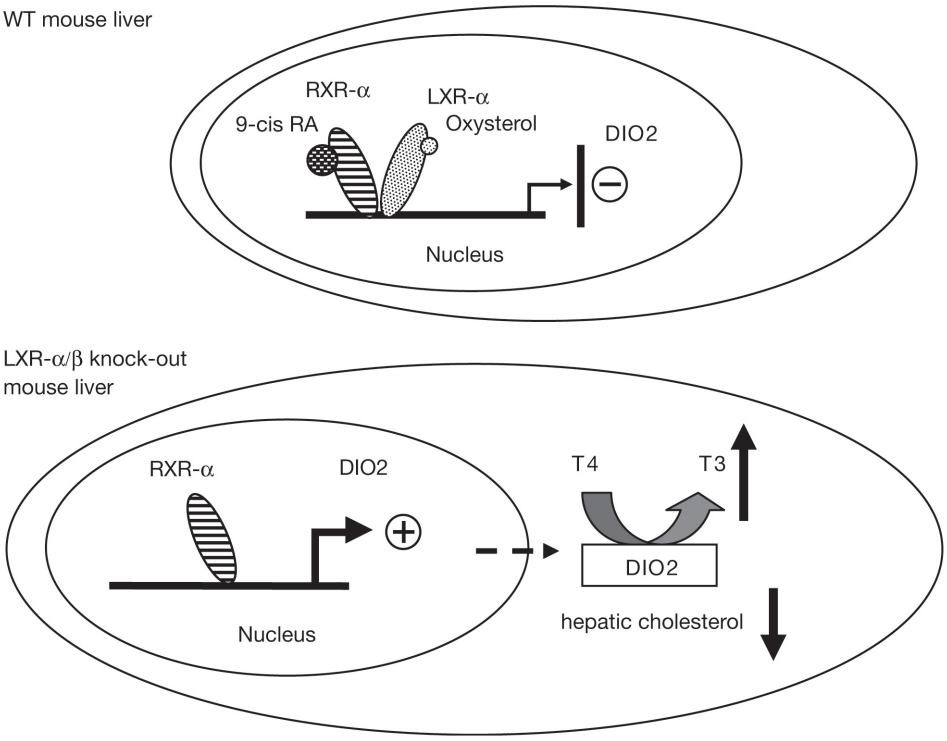

Fig. 4 Ectopic expression of type 2 deiodinase (DIO2) in the liver in LXR-α/β double-knockout mouse
DIO2 is not expressed in wild-type mouse liver since LXR- α negatively regulates DIO2 gene promoter. In the absence of LXR-α/β, ectopic expression of DIO2 in the liver leads to conversion of T4 to T3 followed by hepatic cholesterol reduction.
9-cis RA: 9-cis retinoic acid

pressors to exert their function for transcriptional regulation. These observations suggest similar squelching capacity of corepressor recruitment to TR and LXR on the target genes (Fig. 5).

3 Conclusions and perspective

Part of the mechanism underlying the crosstalk between TRs and LXRs has just been elucidated. It is expected to be revealed that crosstalk could exist on TR and LXR signaling system other than in lipid metabolism such as drug metabolism [50] and neurodegenerative disorders [54, 78]. Future work to identify the TR-LXR crosstalk with different target genes and in other target tissues should be undertaken. Recently, attention has been paid to the fact that both TR and LXR interact with other nuclear receptors [79-81]. We should consider crosstalk among nuclear receptors for analysis of the transcriptional regulation. Further analysis of the crosstalk would surely shed new light on the unknown role of TRs and LXRs in human physiology and diseases.

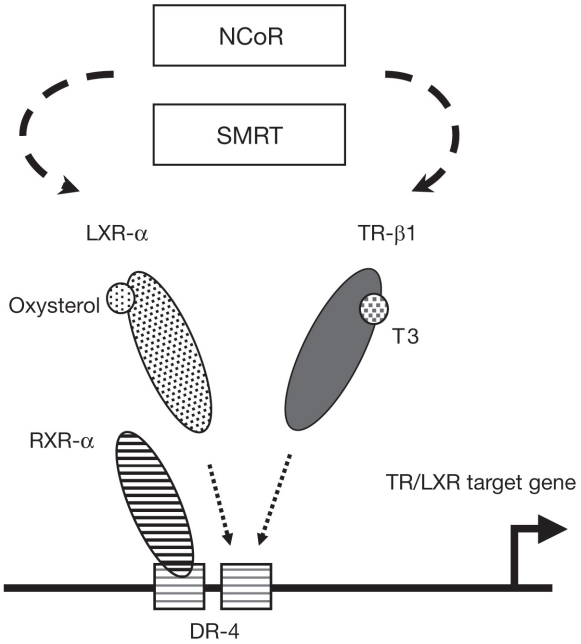

Fig. 5 Crosstalk *via* squelching of co-repressors

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