

International Union of Pharmacology. LIX. The Pharmacology and Classification of the Nuclear Receptor Superfamily: Thyroid Hormone Receptors

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Introduction

The initial identification of thyroid hormone receptors (TRs¹) was based on binding studies (Oppenheimer et al., 1972). The TR main ligand is 3,5,3'-triiodo-L-thyronine (T3). T3 production primarily results from deiodination of thyroxine (T4), which is secreted by the thyroid gland. Most metabolites of T4 and T3 are poor TR ligands except for 3,3',5-triiodo-thyroacetic acid (TRIAC), which is present at very low levels. TRs are encoded by the *THRA* (*NR1A1*) and *THRB* (*NR1A2*) genes. The *THRA* gene was originally identified in chicken as the cellular homolog of the *v-erbA* oncogene (Sap et al., 1986). *THRB* was also cloned by low-stringency screening with the same probe of human and rat cDNA libraries (Weinberger et al., 1986; Thompson et al., 1987). Although mRNA and protein abundance is variable, *THRA* is ubiquitously expressed. *THRB* expression pattern is more restricted and is developmentally regulated. Its main expression sites are the liver, pituitary, inner ear, retina, and several brain areas. The *THRA* promoter possesses a response element for the estrogen receptor-related- α (NR3B1) orphan receptor (Vanacker et al., 1998), and the 3'-end overlaps at its *RevErbA α* (*NR1D1*)-encoding gene, which is transcribed from the antisense DNA strand. The consequences of these features on *THRA* regulation are unclear, although the 3'-end overlap might explain the moderate diurnal variations of TR α 2 isoform protein level observed in the liver

(Zandieh-Doulabi et al., 2003). *THRA* and *THRB* encode the major receptor isoforms TR α 1, TR β 1, and TR β 2 [the TR β 3 receptor (Williams, 2000) is apparently rat-specific], as well as several isoforms unable to bind any ligand (TR α 2, TR α 3, TR $\Delta\alpha$ 1, TR $\Delta\alpha$ 2, and the rat-specific TR $\Delta\beta$ 3). TR α 2 and TR α 3 mRNA results from alternate splicing and differs from TR α 1 at their C terminus. TR $\Delta\alpha$ 1 and TR $\Delta\alpha$ 2 are truncated versions of TR α 1 and TR α 2, respectively, and are translated from mRNA initiated from an internal promoter present in intron 7. In transfected cells, all of these isoforms prevent the T3-induced transcriptional activation mediated by the T3-binding isoforms, but the underlying mechanisms are poorly understood. Alternative translation initiations on the TR α 1 mRNA still provide other isoforms (Bigler et al., 1992). One of these isoforms, p43, has been proposed to be a mitochondrial receptor that regulates mitochondrial transcription (Casas et al., 1999). In vitro data indicate that TR acts mainly as heterodimers with RXR, although TR β 1 homodimers and TR/retinoic acid receptor heterodimers can form (Forman et al., 1992; Lee and Privalsky, 2005). DNA binding of TR/RXR heterodimers is not ligand-dependent and is efficient on DR-4 elements (5'-AGGTCANNNNAGGTCA-3') and inverted palindromes. Although it has been thought that RXR in the TR/RXR heterodimer could not bind its cognate ligand, more recent studies indicate that at least in some cases the RXR ligand 9-cis retinoic acid can influence the activity of the TR/RXR heterodimer (Li et al., 2002) (Castillo et al., 2004; Li et al., 2004).

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¹ Abbreviations: TR, thyroid hormone receptor; T3, 3,5,3'-triiodo-L-thyronine; T4, thyroxine; TRIAC, 3,3',5-triiodo-thyroacetic acid; RXR, retinoid X receptor; DR, direct repeat; RTH, resistance to thyroid hormone; TSH, thyroid-stimulating hormone.

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Structure

X-ray crystallography revealed the structure of the TR ligand-binding domain bound to agonist (Wagner et al., 2001; Borngraeber et al., 2003; Nunes et al., 2004). These data suggest that upon T3 binding the C-terminal helix 12 folds into the scaffold formed by helix 3,4,5, creating a surface with a hydrophobic cleft suitable for

coactivator interaction (Feng et al., 1998; Ribeiro et al., 1998) and preventing corepressor interaction (Marimuthu et al., 2002). The structure of TR/RXR DNA-binding domains bound to a DR-4 element also demonstrate that this spacing between the two binding sites is suitable for optimal RXR/TR dimerization (Rastinejad et al., 1995).

Target Genes

The probably large repertoire of TR target genes remains to be clearly defined. The demonstration that a given gene is directly regulated by TR requires the convergent accumulation of several experimental evidences. Increasing or decreasing T3 levels in cultured cells or living animals should change the mRNA steady-state level T3 regulation and should also be observed in a transient expression assay using an artificial construct, where a fragment of the putative target gene is introduced. The T3 response element(s) present in this DNA fragment should be precisely mapped by deletion analysis. In vitro protein interaction studies should identify the TR-binding site present on this fragment. Finally, it will soon be requested to demonstrate by chromatin immunoprecipitation the actual occupancy by TR of the region containing the T3 response element in a chromosomal context. Very few genes fulfill all the criteria to be considered direct TR targets. The best-known TR target genes encode type 1 deiodinase in liver (Koenig, 2005) and the basic transcription element-binding protein (Morita et al., 2003), Hairless corepressor (Thompson, 1996), and neurogranin (Guadano-Ferraz et al., 1997; Morte et al., 1997) in brain. Recent microarray analyses identified many new putative candidates in liver (Flores-Morales et al., 2002; Yen et al., 2003). Surprisingly, many are down-regulated by T3. For most of these genes, bioinformatics methods did not reveal the presence of consensus DR-4 elements, raising doubts on a direct regulation of these genes by TR. The coming years will tell whether the gap between the microarray data and previous in vitro data can be filled or whether the diversity of TR-mediated regulation has been underestimated.

Pharmacology

T4 and T3 treatment has several potentially beneficial effects, including the lowering of body weight and plasma cholesterol level; however, an excess of T3 provokes bone and muscle loss and a dangerous tachycardia and can lead to atrial arrhythmia. These adverse effects largely counterbalance the possible benefits. One would expect that TR agonists or antagonists would be of great interest if they could act in an isotype isoform or tissue-specific manner. Because T3 is unrelated to all known ligands for other nuclear receptors, T3 analogs might also act on TR without interfering with the ligand domain of other nuclear receptors. It should be kept in

mind, however, that at least in cultured cells T3 and related compounds display a TR-independent activity called nongenomic activity (Davis et al., 2005). GC-1 and KB-141 are the most promising available compounds because they are almost specific for TR β . In animal models, they were found to decrease plasma cholesterol and triglycerides levels and induce fat loss without a visible effect on heart and muscle (Grover et al., 2003; Baxter et al., 2004). Clinical trials are underway for other ligands from the KB series designed by KaroBio with similar properties. Finally, compounds that can rescue functionally impaired TR β receptors may provide new strategies for the treatment of resistance to thyroid hormone (RTH; see "Pathology") (Koh and Biggins, 2005).

Currently, there is no true high-affinity antagonist available for TR (Schapira et al., 2003). The mode of action of the widely used antiarrhythmic drug amiodarone is unclear. Its main metabolite desethylamiodarone is thought to be a weak competitive ligand of T3 for TR α 1 but not for TR β 1. A noncompetitive binding site is postulated to be on the outside surface of the TR β 1 receptor, overlapping the regions where coactivator and corepressor bind. Amiodarone treatment would act by preventing the recruitment of coactivators by TR β 1 (van Beeren et al., 1995, 1996, 2000, 2003). The NH3 compound acts as a relatively specific antagonist; its binding places the TR α 1 receptor in a neutral conformation that does not permit either coactivator or corepressor recruitment (Nguyen et al., 2002, 2005). Other ligands discovered after high throughput screening or in silico virtual screening are currently being evaluated. *O*-Alkyl derivatives of T3 have been synthesized with the aim of stabilizing a nonproductive conformation of key residues in the ligand-binding pocket and thus disfavoring the equilibrium to the agonist conformation of helix-12. Some induce a stabilization of an inactive conformation and lead to an "indirect antagonism" (Hedfors et al., 2005). It has been shown recently that the deamination of some β -aminoketones produce reactive unsaturated ketones that covalently bind to TR, inhibiting TR-coactivator interaction and suppressing its transcriptional activity (Arnold et al., 2005).

Pathology

T3 exerts a pleiotropic effect on development and homeostasis (Yen, 2001). Circulating levels of T4 and T3 in adults are usually very stable. Hyperthyroidism, often a consequence of Graves' disease, can result in goiter, periorbital edema, weight loss, tachycardia, palpitations, muscle weakness, osteoporosis, (especially in postmenopausal women), and mood disorders. Common signs of hypothyroidism are goiter, myxedema, fatigue, cold-intolerance, thinning hair, depression, dry skin, constipation, and bradycardia. If untreated, fetal and neonatal hypothyroidism also limit bone growth and are

responsible for deafness and an irreversible mental retardation called cretinism. Thyroid-related pathology is largely avoidable in developed countries with established neonatal screening for abnormalities in thyroid hormone levels. However, there is growing concern that chemical substances present in food and in the environment might act as thyroid hormone disruptors that alter the circulating levels of T3 and TSH. The permanent exposure to such substances would favor the onset of a number of pathologies and would be harmful for pre- and postnatal brain development (Aoki, 2001; Zoeller et al., 2002). These substances include polychlorinated biphenyls (Zoeller et al., 2000; Gauger et al., 2004), bisphenol A and related compounds (Zoeller et al., 2005), and dioxin and dioxin-like compounds (Nishimura et al., 2003; Viluksela et al., 2004; Yamada-Okabe et al., 2004). The underlying mechanisms are very complex and poorly understood. It seems that some of these molecules act as weak TR ligands (Moriyama et al., 2002; Kitamura et al., 2005).

Human germline mutations are known for *THRB* but not for *THRA*, suggesting that *THRA* mutations might be either lethal or related to unexpected clinical features. *THRB* mutations cause a dominant and polymorphic genetic disease known as RTH (Weiss and Refetoff, 2000; Yen, 2003). Many mutations have been reported that fall into three clusters located in the ligand-binding domain: AA234–282, 310–353, and 429–461 (Collingwood et al., 1998). Almost all of these mutations compromise ligand-binding coactivator recruitment or corepressor release. High levels of T4 and T3 without TSH suppression are typically observed. Inheritance of RTH is dominant since mutant TR β 1 and TR β 2 interfere in a dominant-negative fashion, with the function of wild-type TR β receptors altering feedback regulation on pituitary TSH secretion. Elevated circulating levels of T4 and T3 can create a condition that resembles hyperthyroidism in tissues that mainly express *THRA*. For example, tachycardia may be due to hyperthyroidism in the heart, where cardiomyocytes mainly express *THRA*. The condition is closer to hypothyroidism in tissues that express the mutated *THRB* allele, such as the liver.

Mouse Genetics

A collection of seven mutant alleles for *THRA* and nine mutant alleles for *THRB* that carry either knockout or knockin mutations have been generated over the last 10 years (Forrest and Vennstrom, 2000; Flamant and Samarut, 2003; Wondisford, 2003), and the collection is still growing. Although the diversity of phenotypes is confusing, at first glance the analysis provides a deeper view on TR function in vivo. The following summary conclusions can be drawn.

TR α 1 is a main regulator of development in some tissues during the first weeks of postnatal preweaning development. These 3 weeks are characterized by a peak

of circulating T3 and present some analogies with amphibian metamorphosis. As this point, T3 regulates intestinal remodeling (Plateroti et al., 2001), cerebellum development (Morte et al., 2002), spleen erythropoiesis (Angelin-Duclos et al., 2005), and bone growth (Bassett and Williams, 2003), mainly by activating TR α 1. TR α 1 also has a major role in setting cardiac function and thermogenesis (Wikstrom et al., 1998).

TR β 1 is the main isoform that regulates liver function and the development of hearing, and together with TR β 2, it has a major role in the feedback regulation of the hypothalamic-pituitary-thyroid axis (Forrest et al., 1996a,b). TR β 2 has a specific role in the differentiation of retinal cone photoreceptors required for color vision. TR β 2 also cooperates with TR β 1 in the feedback regulation for the hypothalamic-pituitary-thyroid axis. It may also be involved in the auditory system, but this role can be substituted by TR β 1, which is coexpressed with TR β 2 in the cochlea (Abel et al., 2001; Ng et al., 2001).

Unliganded TR α 1 can regulate gene expression. This function is mainly evidenced by the fact that knocking out *THRA* or both *THRA/THRB* is less detrimental to development than either hypothyroidism (Flamant et al., 2002) or dominant-negative knockin *THRA* mutations (Tinnikov et al., 2002; Liu et al., 2003). Although the possibility for a nongenomic action of T3 should also be considered, these data support the idea that recruitment of corepressor on T3 target genes by unliganded TR α 1 is detrimental to the development of hypothyroid animals. Due to uneven T3 distribution (Quignodon et al., 2004), unliganded TR α 1 might be present in some tissues—even in nonpathological situations. It has been shown to repress cardiac gene expression in fetuses in euthyroid situation (Mai et al., 2004).

The contributions of TR α 1, TR β 1, and TR β 2 to T3 action on a given tissue usually parallels their respective abundance. For example, the liver mainly expresses TR β 1, and microarray data indicate that the *THRB* knockout has a much more visible effect than *THRA* knockout on liver response to T3 (Yen et al., 2003). This difference suggests that, at least at first sight, TR functions are equal and redundant in tissues where they are simultaneously present.

Noncoding isoforms seem to modulate TR function. As discussed previously (Flamant and Samarut, 2003), this function is not clear for TR α 2 but very likely for TR $\Delta\alpha$ 1 and/or TR $\Delta\alpha$ 2. The underlying mechanisms remain poorly understood (Gauthier et al., 2001).

Phenotypic analyses have been performed extensively, and a complete description would go beyond the scope of this review since it seems that every aspect of physiology and postnatal development can be influenced by T3 and TR. The main difficulty of these analyses is to unravel the cell-autonomous consequences of mutations from indirect effects. For example, *THRB* is expressed in the cerebellum only in Purkinje cells, but a *THRB*

knockin mutation affects the proliferation of the neighboring granular cells, suggesting that T3 exerts part of its effect on granular cells indirectly by activating the secretion of trophic factors by Purkinje cells (Hashimoto et al., 2001). The CRE/loxP recombination strategy will certainly provide a new impetus to these studies by allowing for a spatial and temporal control of gene mutations. Some discrepancies also suggest that we are far from a complete understanding of TR action in vivo. For example, two knockin mutations of *THRA* have been made that are a priori-equivalent, but only one of these leads to obesity (Tinnikov et al., 2002; Liu et al., 2003). All of these observations suggest that *THRA*- and *THRB*-somatic and -germline mutations might be involved in a much larger number of human pathological conditions, including cancer (Cheng, 2003), than it is usually assumed and that new TR ligands will find many applications.

Tables 1 and 2 describe the major molecular, physiological, and pharmacological properties of TR α and TR β , respectively.

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REFERENCES

- Abel ED, Ahima RS, Boers ME, Elmquist JK, and Wondisford FE (2001) Critical role for thyroid hormone receptor beta2 in the regulation of paraventricular thyrotropin-releasing hormone neurons. *J Clin Invest* **107**:1017–1023.
- Angelin-Duclos C, Domenget C, Kolbus A, Beug H, Jurdic P, and Samarut J (2005) Thyroid hormone T3 acting through the thyroid hormone alpha receptor is necessary for implementation of erythropoiesis in the neonatal spleen environment in the mouse. *Development* **132**:925–934.
- Aoki Y (2001) Polychlorinated biphenyls polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as endocrine disruptors—what we have learned from Yusho disease. *Environ Res* **86**:2–11.
- Arnold LA, Estebanez-Perpina E, Togashi M, Jouravel N, Shelat A, McReynolds AC, Mar E, Nguyen P, Baxter JD, Fletterick RJ, et al. (2005) Discovery of small molecule inhibitors of the interaction of thyroid hormone receptor with transcriptional coregulators. *J Biol Chem* **280**:43048–43055.
- Bassett JH and Williams GR (2003) The molecular actions of thyroid hormone in bone. *Trends Endocrinol Metab* **14**:356–364.
- Baxter JD, Webb P, Grover G, and Scanlan TS (2004) Selective activation of thyroid hormone signaling pathways by GC-1: a new approach to controlling cholesterol and body weight. *Trends Endocrinol Metab* **15**:154–157.
- Bigler J, Hokanson W, and Eisenman RN (1992) Thyroid hormone receptor transcriptional activity is potentially autoregulated by truncated forms of the receptor. *Mol Cell Biol* **12**:2406–2417.
- Borngraeber S, Budny MJ, Chiellini G, Cunha-Lima ST, Togashi M, Webb P, Baxter JD, Scanlan TS, and Fletterick RJ (2003) Ligand selectivity by seeking hydrophobicity in thyroid hormone receptor. *Proc Natl Acad Sci USA* **100**:15358–15363.
- Casas F, Rochard P, Rodier A, Cassar-Malek I, Marchal-Victorin S, Wiesner RJ, Cabello G, and Wrutniak C (1999) A variant form of the nuclear triiodothyronine receptor c-ErbAalpha1 plays a direct role in regulation of mitochondrial RNA synthesis. *Mol Cell Biol* **19**:7913–7924.
- Castillo AI, Sanchez-Martinez R, Moreno JL, Martinez-Iglesias OA, Palacios D, and Aranda A (2004) A permissive retinoid X receptor/thyroid hormone receptor heterodimer allows stimulation of prolactin gene transcription by thyroid hormone and 9-cis-retinoic acid. *Mol Cell Biol* **24**:502–513.
- Cheng SY (2003) Thyroid hormone receptor mutations in cancer. *Mol Cell Endocrinol* **213**:23–30.
- Collingwood TN, Wagner R, Matthews CH, Clifton-Bligh RJ, Gurnell M, Rajanayagam O, Agostini M, Fletterick RJ, Beck-Peccoz P, Reinhardt W, et al. (1998) A role for helix 3 of the TRbeta ligand-binding domain in coactivator recruitment identified by characterization of a third cluster of mutations in resistance to thyroid hormone. *EMBO (Eur Mol Biol Organ) J* **17**:4760–4770.
- Davis PJ, Davis FB, and Cody V (2005) Membrane receptors mediating thyroid hormone action. *Trends Endocrinol Metab* **16**:429–435.
- Feng W, Ribeiro RC, Wagner RL, Nguyen H, Apriletti JW, Fletterick RJ, Baxter JD, Kushner PJ, and West BL (1998) Hormone-dependent coactivator binding to a hydrophobic cleft on nuclear receptors. *Science (Wash DC)* **280**:1747–1749.
- Flamant F, Poguet AL, Plateroti M, Chassande O, Gauthier K, Streichenberger N, Mansouri A, and Samarut J (2002) Congenital hypothyroid Pax8(–/–) mutant mice can be rescued by inactivating the TRalpha gene. *Mol Endocrinol* **16**:24–32.
- Flamant F and Samarut J (2003) Thyroid hormone receptors: lessons from knockout and knock-in mutant mice. *Trends Endocrinol Metab* **14**:85–90.
- Flores-Morales A, Gullberg H, Fernandez L, Stahlberg N, Lee NH, Vennstrom B, and Norstedt G (2002) Patterns of liver gene expression governed by TRbeta. *Mol Endocrinol* **16**:1257–1268.
- Forman BM, Casanova J, Raaka BM, Ghysdael J, and Samuels HH (1992) Half-site spacing and orientation determines whether thyroid hormone and retinoic acid receptors and related factors bind to DNA response elements as monomers homodimers or heterodimers. *Mol Endocrinol* **6**:429–442.
- Forrest D, Erway LC, Ng L, Altschuler R, and Curran T (1996a) Thyroid hormone receptor beta is essential for development of auditory function. *Nat Genet* **13**:354–357.
- Forrest D, Hanebuth E, Smeysne RJ, Everds N, Stewart CL, Wehner JM, and Curran T (1996b) Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. *EMBO (Eur Mol Biol Organ) J* **15**:3006–3015.
- Forrest D and Vennstrom B (2000) Functions of thyroid hormone receptors in mice. *Thyroid* **10**:41–52.
- Gauger KJ, Kato Y, Haraguchi K, Lehmler HJ, Robertson LW, Bansal R, and Zoeller RT (2004) Polychlorinated biphenyls (PCBs) exert thyroid hormone-like effects in the fetal rat brain but do not bind to thyroid hormone receptors. *Environ Health Perspect* **112**:516–523.
- Gauthier K, Plateroti M, Harvey CB, Williams GR, Weiss RE, Refetoff S, Willott JF, Sundin V, Roux JP, Malaval L, et al. (2001) Genetic analysis reveals different functions for the products of the thyroid hormone receptor alpha locus. *Mol Cell Biol* **21**:4748–4760.
- Grover GJ, Mellstrom K, Ye L, Malm J, Li YL, Bladh LG, Sleph PG, Smith MA, George R, Vennstrom B, et al. (2003) Selective thyroid hormone receptor-beta activation: a strategy for reduction of weight cholesterol and lipoprotein (a) with reduced cardiovascular liability. *Proc Natl Acad Sci USA* **100**:10067–10072.
- Guadano-Ferraz A, Escamez MJ, Morte B, Vargiu P, and Bernal J (1997) Transcriptional induction of RC3/neurogranin by thyroid hormone: differential neuronal sensitivity is not correlated with thyroid hormone receptor distribution in the brain. *Brain Res Mol Brain Res* **49**:37–44.
- Hashimoto K, Curtly FH, Borges PP, Lee CE, Abel ED, Elmquist JK, Cohen RN, and Wondisford FE (2001) An unliganded thyroid hormone receptor causes severe neurological dysfunction. *Proc Natl Acad Sci USA* **98**:3998–4003.
- Hedfors A, Appelqvist T, Carlsson B, Bladh LG, Litten C, Agback P, Grynfarb M, Koehler KF, and Malm J (2005) Thyroid receptor ligands. 3. Design and synthesis of 3,5-dihalo-4-alkoxyphenylalkanoic acids as indirect antagonists of the thyroid hormone receptor. *J Med Chem* **48**:3114–3117.
- Kitamura S, Kato T, Iida M, Jinno N, Suzuki T, Ohta S, Fujimoto N, Hanada H, Kashiwagi K, and Kashiwagi A (2005) Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: affinity to the mammalian thyroid hormone receptor and effect on tadpole metamorphosis. *Life Sci* **76**:1589–1601.
- Koenig RJ (2005) Regulation of type 1 iodothyronine deiodinase in health and disease. *Thyroid* **15**:835–840.
- Koh JT and Biggins JB (2005) Ligand-receptor engineering and its application towards the complementation of genetic disease and target identification. *Curr Top Med Chem* **5**:413–420.
- Lee S and Privalsky ML (2005) Heterodimers of retinoic acid receptors and thyroid hormone receptors display unique combinatorial regulatory properties. *Mol Endocrinol* **19**:863–878.
- Li D, Li T, Wang F, Tian H, and Samuels HH (2002) Functional evidence for retinoid X receptor (RXR) as a nonsilent partner in the thyroid hormone receptor/RXR heterodimer. *Mol Cell Biol* **22**:5782–5792.
- Li D, Yamada T, Wang F, Vulin AI, and Samuels HH (2004) Novel roles of retinoid X receptor (RXR) and RXR ligand in dynamically modulating the activity of the thyroid hormone receptor/RXR heterodimer. *J Biol Chem* **279**:7427–7437.
- Liu YY, Schultz JJ, and Brent GA (2003) A thyroid hormone receptor alpha gene mutation (P398H) is associated with visceral adiposity and impaired catecholamine-stimulated lipolysis in mice. *J Biol Chem* **278**:38913–38920.
- Mai W, Janier MF, Allioli N, Quignodon L, Chuzel T, Flamant F, and Samarut J (2004) Thyroid hormone receptor alpha is a molecular switch of cardiac function between fetal and postnatal life. *Proc Natl Acad Sci USA* **101**:10332–10337.
- Marimuthu A, Feng W, Tagami T, Nguyen H, Jameson JL, Fletterick RJ, Baxter JD, and West BL (2002) TR surfaces and conformations required to bind nuclear receptor corepressor. *Mol Endocrinol* **16**:271–286.
- Morita M, Kobayashi A, Yamashita T, Shimanuki T, Nakajima O, Takahashi S, Ikegami S, Inokuchi K, Yamashita K, Yamamoto M, et al. (2003) Functional analysis of basic transcription element binding protein by gene targeting technology. *Mol Cell Biol* **23**:2489–2500.
- Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, Hataya Y, Shimatsu A, Kuzuya H, and Nakao K (2002) Thyroid hormone action is disrupted by bisphenol A as an antagonist. *J Clin Endocrinol Metab* **87**:5185–5190.
- Morte B, Iniguez MA, Lorenzo PI, and Bernal J (1997) Thyroid hormone-regulated expression of RC3/neurogranin in the immortalized hypothalamic cell line GT1-7. *J Neurochem* **69**:902–909.
- Morte B, Manzano J, Scanlan T, Vennstrom B, and Bernal J (2002) Deletion of the thyroid hormone receptor alpha 1 prevents the structural alterations of the cerebellum induced by hypothyroidism. *Proc Natl Acad Sci USA* **99**:3985–3989.
- Ng L, Hurler JB, Dierks B, Srinivas M, Salto C, Vennstrom B, Reh TA, and Forrest

- D (2001) A thyroid hormone receptor that is required for the development of green cone photoreceptors. *Nat Genet* **27**:94–98.
- Nguyen NH, Apreletti JW, Baxter JD, and Scanlan TS (2005) Hammett analysis of selective thyroid hormone receptor modulators reveals structural and electronic requirements for hormone antagonists. *J Am Chem Soc* **127**:4599–4608.
- Nguyen NH, Apreletti JW, Cunha Lima ST, Webb P, Baxter JD, and Scanlan TS (2002) Rational design and synthesis of a novel thyroid hormone antagonist that blocks coactivator recruitment. *J Med Chem* **45**:3310–3320.
- Nishimura N, Yonemoto J, Miyabara Y, Sato M, and Tohyama C (2003) Rat thyroid hyperplasia induced by gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Endocrinology* **144**:2075–2083.
- Nunes FM, Aparicio R, Santos MA, Portugal RV, Dias SM, Neves FA, Simeoni LA, Baxter JD, Webb P, and Polikarpov I (2004) Crystallization and preliminary X-ray diffraction studies of isoform alpha1 of the human thyroid hormone receptor ligand-binding domain. *Acta Crystallogr D Biol Crystallogr* **60**:1867–1870.
- Oppenheimer JH, Koerner K, Schwartz HL, and Surks MI (1972) Specific nuclear triiodothyronine binding sites in rat liver and kidney. *J Clin Endocrinol Metab* **35**:330–333.
- Plateroti M, Gauthier K, Domon-Dell C, Freund JN, Samarut J, and Chassande O (2001) Functional interference between thyroid hormone receptor alpha (TRalpha) and natural truncated TRdeltaalpha isoforms in the control of intestine development. *Mol Cell Biol* **21**:4761–4772.
- Quignodon L, Legrand C, Allioli N, Guadano-Ferraz A, Bernal J, Samarut J, and Flamant F (2004) Thyroid hormone signaling is highly heterogeneous during pre- and postnatal brain development. *J Mol Endocrinol* **33**:467–476.
- Rastinejad F, Perlmann T, Evans RM, and Sigler PB (1995) Structural determinants of nuclear receptor assembly on DNA direct repeats. *Nature (Lond)* **375**:203–211.
- Ribeiro RC, Apreletti JW, Wagner RL, Feng W, Kushner PJ, Nilsson S, Scanlan TS, West BL, Fletterick RJ, and Baxter JD (1998) X-ray crystallographic and functional studies of thyroid hormone receptor. *J Steroid Biochem Mol Biol* **65**:133–141.
- Sap J, Munoz A, Damm K, Goldberg Y, Ghysdael J, Leutz A, Beug H, and Vennstrom B (1986) The c-erb-A protein is a high-affinity receptor for thyroid hormone. *Nature (Lond)* **324**:635–640.
- Schapiro M, Raaka BM, Das S, Fan L, Totrov M, Zhou Z, Wilson SR, Abagyan R, and Samuels HH (2003) Discovery of diverse thyroid hormone receptor antagonists by high-throughput docking. *Proc Natl Acad Sci USA* **100**:7354–7359.
- Thompson CC (1996) Thyroid hormone-responsive genes in developing cerebellum include a novel synaptotagmin and a hairless homolog. *J Neurosci* **16**:7832–7840.
- Thompson CC, Weinberger C, Lebo R, and Evans RM (1987) Identification of a novel thyroid hormone receptor expressed in the mammalian central nervous system. *Science (Wash DC)* **237**:1610–1614.
- Tinnikov A, Nordström K, Thoren P, Kindblom JM, Malin S, Rozell B, Adams M, Rajanayagam O, Petterson S, Ohlsson C, et al. (2002) Retardation of post-natal development caused by a negatively acting thyroid receptor alpha1. *EMBO (Eur Mol Biol Organ) J* **21**:1–9.
- van Beeren HC, Bakker O, and Wiersinga WM (1995) Desethylamiodarone is a competitive inhibitor of the binding of thyroid hormone to the thyroid hormone alpha 1-receptor protein. *Mol Cell Endocrinol* **112**:15–19.
- van Beeren HC, Bakker O, and Wiersinga WM (1996) Structure-function relationship of the inhibition of the 3,5,3'-triiodothyronine binding to the alpha1- and beta1-thyroid hormone receptor by amiodarone analogs. *Endocrinology* **137**:2807–2814.
- van Beeren HC, Bakker O, and Wiersinga WM (2000) Desethylamiodarone interferes with the binding of co-activator GRIP-1 to the beta 1-thyroid hormone receptor. *FEBS Lett* **481**:213–216.
- van Beeren HC, Jong WM, Kaptein E, Visser TJ, Bakker O, Wiersinga WM, Zandieh Doulabi B, Platvoet-ter Schiphorst M, Labruyere WT, Lamers WH, et al. (2003) Dronerone acts as a selective inhibitor of 3,5,3'-triiodothyronine binding to thyroid hormone receptor-alpha(1): in vitro and in vivo evidence. *Endocrinology* **144**:552–558.
- Vanacker JM, Bonnelye E, Delmarre C, and Laudet V (1998) Activation of the thyroid hormone receptor alpha gene promoter by the orphan nuclear receptor ERR alpha. *Oncogene* **17**:2429–2435.
- Viluksela M, Raasmaja A, Lebofsky M, Stahl BU, and Rozman KK (2004) Tissue-specific effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the activity of 5'-deiodinases I and II in rats. *Toxicol Lett* **147**:133–142.
- Wagner RL, Huber BR, Shiao AK, Kelly A, Cunha Lima ST, Scanlan TS, Apreletti JW, Baxter JD, West BL, and Fletterick RJ (2001) Hormone selectivity in thyroid hormone receptors. *Mol Endocrinol* **15**:398–410.
- Weinberger C, Thompson CC, Ong ES, Lebo R, Gruol DJ, and Evans RM (1986) The c-erb-A gene encodes a thyroid hormone receptor. *Nature (Lond)* **324**:641–646.
- Weiss RE and Refetoff S (2000) Resistance to thyroid hormone. *Rev Endocr Metab Disord* **1**:97–108.
- Wikstrom L, Johansson C, Salto C, Barlow C, Campos Barros A, Baas F, Forrest D, Thoren P, and Vennstrom B (1998) Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. *EMBO (Eur Mol Biol Organ) J* **17**:455–461.
- Williams GR (2000) Cloning and characterization of two novel thyroid hormone receptor beta isoforms. *Mol Cell Biol* **20**:8329–8342.
- Wondisford FE (2003) Thyroid hormone action: insight from transgenic mouse models. *J Invest Med* **51**:215–220.
- Yamada-Okabe T, Aono T, Sakai H, Kashima Y, and Yamada-Okabe H (2004) 2,3,7,8-tetrachlorodibenzo-p-dioxin augments the modulation of gene expression mediated by the thyroid hormone receptor. *Toxicol Appl Pharmacol* **194**:201–210.
- Yen PM (2001) Physiological and molecular basis of thyroid hormone action. *Physiol Rev* **81**:1097–1142.
- Yen PM (2003) Molecular basis of resistance to thyroid hormone. *Trends Endocrinol Metab* **14**:327–333.
- Yen PM, Feng X, Flamant F, Chen Y, Walker RL, Weiss RE, Chassande O, Samarut J, Refetoff S, and Meltzer PS (2003) Effects of ligand and thyroid hormone receptor isoforms on hepatic gene expression profiles of thyroid hormone receptor knockout mice. *EMBO Rep* **4**:581–587.
- Zandieh-Doulabi B, Dop E, Schneiders M, Schiphorst MP, Mansen A, Vennstrom B, Dijkstra CD, Bakker O, and Wiersinga WM (2003) Zonal expression of the thyroid hormone receptor alpha isoforms in rodent liver. *J Endocrinol* **179**:379–385.
- Zoeller RT, Bansal R, and Parris C (2005) Bisphenol-A, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters RC3/neurogranin expression in the developing rat brain. *Endocrinology* **146**:607–612.
- Zoeller RT, Dowling AL, and Vas AA (2000) Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. *Endocrinology* **141**:181–189.
- Zoeller TR, Dowling AL, Herzig CT, Iannacone EA, Gauger KJ, and Bansal R (2002) Thyroid hormone brain development and the environment. *Environ Health Perspect* **110 (Suppl 3)**:355–361.

TABLE 1
TR α

Receptor nomenclature	NR1A1
Receptor code	4.10.1:TH:A1
Other names	THRA, c-erbA α
Molecular information	Hs: 410aa, P10827, chr. 17q11.2 ¹ Rn: 410aa, P63059, chr. 10q31 ² Mm: 410aa, Q542U8, chr. 11 D-E ³
DNA binding	
Structure	Monomer, heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-4, palindrome)
Agonists	TRAC (154), T4 (14), reverse T3 (0.11) ⁴ ; T3* (58 pM), GC-1 (440 pM) [K _d] ^{5,6}
Antagonists	NH ₃ (20 nM) [K _d] ⁵
Coactivators	NCOA1, NCOA2, NCOA3, PPARBP ⁷⁻¹⁰
Corepressors	NCOR1, NCOR2 ^{11,12}
Biologically important isoforms	TR α 1(Hs, Mm, Rn): main isoform; TR α 2(Hs, Mm, Rn): splice variant, DNA binding but no T3 binding, acts as antagonist ^{13,14} ; TR δ 1(Hs, Mm, Rn): truncated, no DNA or T3 binding, acts as antagonist ¹⁵ ; TR δ 2(Hs, Mm, Rn): truncated, no DNA or T3 binding, acts as antagonist ¹⁵ ; TR α 3(Mm): splice variant, DNA binding but no T3 binding ¹⁶
Tissue distribution	Ubiquitous {Hs, Mm, Rn} [in situ hybridization] ¹⁷
Functional assays	Heart response {Mm} ¹⁸
Main target genes	Activated: <i>Hr</i> {Mm}, <i>Hcn2</i> {Mm} ^{19,20}
Mutant phenotype	Pleiotropic; usually viable and fertile {Mm} [knockout] ^{18,21,22} ; knockin mutation-changing AF2 domain results in dwarfism and obesity {Mm} [knockin] ^{23,24}

aa, amino acids; chr., chromosome; PPARBP, peroxisome proliferator-activated receptor binding protein.

* Radioligand.

1. Masuda M, Yasuhara S, Yamashita M, Shibuya M, and Odaka T (1990) Nucleotide sequence of the murine thyroid hormone receptor (alpha-1) cDNA. *Nucleic Acids Res* **18**:3055.

2. Murray MB, Zilz ND, McCreary NL, MacDonald MJ, and Towle HC (1988) Isolation and characterization of rat cDNA clones for two distinct thyroid hormone receptors. *J Biol Chem* **263**:12770-12777.

3. Wood WM, Ocran KW, Gordon DF, and Ridgway EC (1991) Isolation and characterization of mouse complementary DNAs encoding alpha and beta thyroid hormone receptors from thyrotrope cells: the mouse pituitary-specific beta 2 isoform differs at the amino terminus from the corresponding species from rat pituitary tumor cells. *Mol Endocrinol* **5**:1049-1061.

4. Schueler PA, Schwartz HL, Strait KA, Mariash CN, and Oppenheimer JH (1990) Binding of 3,5,3'-triiodothyronine (T3) and its analogs to the in vitro translational products of c-erbA protooncogenes: differences in the affinity of the alpha- and beta-forms for the acetic acid analog and failure of the human testis and kidney alpha-2 products to bind T3. *Mol Endocrinol* **4**:227-234.

5. Nguyen NH, Apriletti JW, Cunha Lima ST, Webb P, Baxter JD, and Scanlan TS (2002) Rational design and synthesis of a novel thyroid hormone antagonist that blocks coactivator recruitment. *J Med Chem* **45**:3310-3320.

6. Sharma D and Fondell JD (2002) Ordered recruitment of histone acetyltransferases and the TRAP/Mediator complex to thyroid hormone-responsive promoters in vivo. *Proc Natl Acad Sci USA* **99**:7934-7939.

7. Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, and Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* **90**:569-580.

8. Ito M, Yuan CX, Okano HJ, Darnell RB, and Roeder RG (2000) Involvement of the TRAP220 component of the TRAP/SMCC coactivator complex in embryonic development and thyroid hormone action. *Mol Cell* **5**:683-693.

9. Ma H, Hong H, Huang SM, Irvine RA, Webb P, Kushner PJ, Coetzee GA, and Stallcup MR (1999) Multiple signal input and output domains of the 160-kilodalton nuclear receptor coactivator proteins. *Mol Cell Biol* **19**:6164-6173.

10. Nevado J, Tenbaum SP, and Aranda A (2004) hSrb7, an essential human Mediator component, acts as a coactivator for the thyroid hormone receptor. *Mol Cell Endocrinol* **222**:41-51.

11. Chen JD and Evans RM (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. *Nature (Lond)* **377**:454-457.

12. Horlein AJ, Naar AM, Heinzl T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Soderstrom M, Glass CK, et al. (1995) Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. *Nature (Lond)* **377**:397-404.

13. Mitsuhashi T, Tennyson GE, and Nikodem VM (1998) Alternative splicing generates messages encoding rat c-erbA proteins that do not bind thyroid hormone. *Proc Natl Acad Sci USA* **85**:5804-5808.

14. Nakai A, Seino S, Sakurai A, Szilak I, Bell GI, and DeGroot LJ (1998) Characterization of a thyroid hormone receptor expressed in human kidney and other tissues. *Proc Natl Acad Sci USA* **85**:2781-2785.

15. Chassande O, Fraichard A, Gauthier K, Flamant F, Legrand C, Savatier P, Laudet V, and Samarut J (1997) Identification of transcripts initiated from an internal promoter in the c-erbA alpha locus that encode inhibitors of retinoic acid receptor-alpha and triiodothyronine receptor activities. *Mol Endocrinol* **11**:1278-1290.

16. Prost E, Koenig RJ, Moore DD, Larsen PR, and Whalen RG (1988) Multiple sequences encoding potential thyroid hormone receptors isolated from mouse skeletal muscle cDNA libraries. *Nucleic Acids Res* **16**:6248.

17. Gray PA, Fu H, Luo P, Zhao Q, Yu J, Ferrari A, Tenzen T, Yuk DI, Tsung EF, Cai Z, et al. (2004) Mouse brain organization revealed through direct genome-scale TF expression analysis. *Science* **306**:2255-2257.

18. Wikstrom L, Johansson C, Salto C, Barlow C, Campos Barros A, Baas F, Forrest D, Thoren P, and Vennstrom B (1998) Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. *EMBO (Eur Mol Biol Organ) J* **17**:455-461.

19. Gloss B, Sayen MR, Trost SU, Bluhm WF, Meyer M, Swanson EA, Usala SJ, and Dillmann WH (1999) Altered cardiac phenotype in transgenic mice carrying the delta337 threonine thyroid hormone receptor beta mutant derived from the S family. *Endocrinology* **140**:897-902.

20. Thompson CC (1996) Thyroid hormone-responsive genes in developing cerebellum include a novel synaptotagmin and a hairless homolog. *J Neurosci* **16**:7832-7840.

21. Fraichard A, Chassande O, Plateroti M, Roux JP, Trouillas J, Dehay C, Legrand C, Gauthier K, Keding M, Malaval L, et al. (1997) The T3R alpha gene encoding a thyroid hormone receptor is essential for post-natal development and thyroid hormone production. *EMBO (Eur Mol Biol Org) J* **16**:4412-4420.

22. Gauthier K, Chassande O, Plateroti M, Roux JP, Legrand C, Pain B, Rousset B, Weiss R, Trouillas J, and Samarut J (1999) Different functions for the thyroid hormone receptors TRalpha and TRbeta in the control of thyroid hormone production and post-natal development. *EMBO (Eur Mol Biol Org) J* **18**:623-631.

23. Liu YY, Schultz JJ, and Brent GA (2003) A thyroid hormone receptor alpha gene mutation (P398H) is associated with visceral adiposity and impaired catecholamine-stimulated lipolysis in mice. *J Biol Chem* **278**:38913-38920.

24. Tinnikov A, Nordström K, Thoren P, Kindblom JM, Malin S, Rozell B, Adams M, Rajanayagam O, Petterson S, Ohlsson C, et al. (2002) Retardation of post-natal development caused by a negatively acting thyroid receptor alpha1. *EMBO (Eur Mol Biol Org) J* **21**:1-9.

TABLE 2
TR β

Receptor nomenclature	NR1A2
Receptor code	4.10.1:TH:B1
Other names	THRB, c-erbA β
Molecular information	Hs: 461aa, P10828, chr. 3p24.3 ¹ Rn: 461aa, P18113, chr. 15p16 ² Mm: 461aa, P37242, chr. 14 A3 ³
DNA binding	
Structure	Homodimer, heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-4, palindrome)
Agonists	TRiAc (20 pM), GC-1* (67 pM), T3 (81 pM), T4 (3 nM), reverse T3 (46 nM) [K_d] ⁴⁻⁶
Antagonists	NH ₃ (93 nM) [K_d] ⁶
Coactivators	NCOA1, NCOA2, NCOA3, PPARBP ⁷⁻¹⁰
Corepressors	NCOR1, NCOR2 ^{11,12}
Biologically important isoforms	Tr β 1 {Hs, Mm, Rn}: main isoform in most cases; Tr β 2 {Hs, Mm, Rn}: alternative promoter usage, N-terminal variant ¹³ ; Tr β 3 {Rn}: alternative promoter usage and splicing ¹⁴ ; TR $\delta\beta$ 3 {Rn}: alternative promoter usage and splicing ¹⁴
Tissue distribution	Liver, heart, several brain areas {Hs, Mm, Rn} [Northern blot, Q-PCR] ¹⁵
Functional assays	Type 1 deiodinase expression in the liver {Mm} ¹⁶
Main target genes	Activated: <i>Dio1</i> {Mm} ¹⁶ ; repressed: <i>Tshb</i> {Mm} ¹⁷
Mutant phenotype	Deafness, color perception, elevated T3 level {Mm} [knockout] ¹⁸⁻²² ; deafness, elevated T3 level, cerebellum development {Mm} [knockin] ^{17,23,24} ; resistance to thyroid hormone {Mm} [point mutation] ²⁵
Human disease	Resistance to thyroid hormones

aa, amino acids; chr., chromosome; Q-PCR, quantitative polymerase chain reaction; PPARBP, peroxisome proliferator-activated receptor binding protein.

* Radioligand.

- Weinberger C, Thompson CC, Ong ES, Lebo R, Gruol DJ, and Evans RM (1986) The c-erb-A gene encodes a thyroid hormone receptor. *Nature (Lond)* **324**:641-646.
- Thompson CC, Weinberger C, Lebo R, and Evans RM (1987) Identification of a novel thyroid hormone receptor expressed in the mammalian central nervous system. *Science* **237**:1610-1614.
- Wood WM, Ocran KW, Gordon DF, and Ridgway EC (1991) Isolation and characterization of mouse complementary DNAs encoding alpha and beta thyroid hormone receptors from thyrotrope cells: the mouse pituitary-specific beta 2 isoform differs at the amino terminus from the corresponding species from rat pituitary tumor cells. *Mol Endocrinol* **5**:1049-1061.
- Schueler PA, Schwartz HL, Strait KA, Mariash CN, and Oppenheimer JH (1990) Binding of 3,5,3'-triiodothyronine (T3) and its analogs to the in vitro translational products of c-erbA protooncogenes: differences in the affinity of the alpha- and beta-forms for the acetic acid analog and failure of the human testis and kidney alpha-2 products to bind T3. *Mol Endocrinol* **4**:227-234.
- Sharma D and Fondell JD (2002) Ordered recruitment of histone acetyltransferases and the TRAP/Mediator complex to thyroid hormone-responsive promoters in vivo. *Proc Natl Acad Sci USA* **99**:7934-7939.
- Nguyen NH, Apriletti JW, Cunha Lima ST, Webb P, Baxter JD, and Scanlan TS (2002) Rational design and synthesis of a novel thyroid hormone antagonist that blocks coactivator recruitment. *J Med Chem* **45**:3310-3320.
- Nevado J, Tenbaum SP, and Aranda A (2004) hSrb7, an essential human Mediator component, acts as a coactivator for the thyroid hormone receptor. *Mol Cell Endocrinol* **222**:41-51.
- Ma H, Hong H, Huang SM, Irvine RA, Webb P, Kushner PJ, Coetzee GA, and Stallcup MR (1999) Multiple signal input and output domains of the 160-kilodalton nuclear receptor coactivator proteins. *Mol Cell Biol* **19**:6164-6173.
- Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, and Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* **90**:569-580.
- Ito M, Yuan CX, Okano HJ, Darnell RB, and Roeder RG (2000) Involvement of the TRAP220 component of the TRAP/SMCC coactivator complex in embryonic development and thyroid hormone action. *Mol Cell* **5**:683-693.
- Chen JD and Evans RM (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. *Nature (Lond)* **377**:454-457.
- Horlein AJ, Naar AM, Heinzl T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Soderstrom M, Glass CK, et al. (1995) Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. *Nature (Lond)* **377**:397-404.
- Lazar MA and Chin WW (1990) Nuclear thyroid hormone receptors. *J Clin Invest* **86**:1777-1782.
- Williams GR (2000) Cloning and characterization of two novel thyroid hormone receptor beta isoforms. *Mol Cell Biol* **20**:8329-8342.
- Iskaros J, Pickard M, Evans I, Sinha A, Hardiman P, and Ekins R (2000) Thyroid hormone receptor gene expression in first trimester human fetal brain. *J Clin Endocrinol Metab* **85**:2620-2623.
- Zavacki AM, Ying H, Christoffolete MA, Aerts G, So E, Harney JW, Cheng SY, Larsen PR, and Bianco AC (2005) Type 1 iodothyronine deiodinase is a sensitive marker of peripheral thyroid status in the mouse. *Endocrinology* **146**:1568-1575.
- Shibusawa N, Hollenberg AN, and Wondisford FE (2003) Thyroid hormone receptor DNA binding is required for both positive and negative gene regulation. *J Biol Chem* **278**:732-738.
- Forrest D, Erway LC, Ng L, Altschuler R, and Curran T (1996) Thyroid hormone receptor beta is essential for development of auditory function. *Nat Genet* **13**:354-357.
- Forrest D, Hanebuth E, Smeyne RJ, Evers N, Stewart CL, Wehner JM, and Curran T (1996) Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. *EMBO (Eur Mol Biol Org) J* **15**:3006-3015.
- Gauthier K, Chassande O, Plateroti M, Roux JP, Legrand C, Pain B, Rousset B, Weiss R, Trouillas J, and Samarut J (1999) Different functions for the thyroid hormone receptors TRalpha and TRbeta in the control of thyroid hormone production and post-natal development. *EMBO (Eur Mol Biol Org) J* **18**:623-631.
- Abel ED, Boers ME, Pazos-Moura C, Moura E, Kaulbach H, Zakaria M, Lowell B, Radovick S, Liberman MC, and Wondisford F (1999) Divergent roles for thyroid hormone receptor beta isoforms in the endocrine axis and auditory system. *J Clin Invest* **104**:291-300.
- Ng L, Hurlley JB, Dierks B, Srinivas M, Salto C, Vennstrom B, Reh TA, and Forrest D (2001) A thyroid hormone receptor that is required for the development of green cone photoreceptors. *Nat Genet* **27**:94-98.
- Hashimoto K, Curty FH, Borges PP, Lee CE, Abel ED, Elmquist JK, Cohen RN, and Wondisford FE (2001) An unliganded thyroid hormone receptor causes severe neurological dysfunction. *Proc Natl Acad Sci USA* **98**:3998-4003.
- Kaneshige M, Kaneshige K, Zhu X, Dace A, Garrett L, Carter TA, Kazlauskaitis R, Pankratz DG, Wynshaw-Boris A, Refetoff S, et al. (2000) Mice with a targeted mutation in the thyroid hormone beta receptor gene exhibit impaired growth and resistance to thyroid hormone. *Proc Natl Acad Sci USA* **97**:13209-13214.
- Weiss RE and Refetoff S (2000) Resistance to thyroid hormone. *Rev Endocr Metab Disord* **1**:97-108.