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Our understanding of thyroid hormone action has been substantially altered by recent clinical observations of thyroid signaling defects in syndromes of hormone resistance and in a broad range of conditions, including profound mental retardation, obesity, metabolic disorders, and a number of cancers. The mechanism of thyroid hormone action has been informed by these clinical observations as well as by animal models and has influenced the way we view the role of local ligand availability; tissue and cell-specific thyroid hormone transporters, corepressors, and coactivators; thyroid hormone receptor (TR) isoform–specific action; and cross-talk in metabolic regulation and neural development. In some cases, our new understanding has already been translated into therapeutic strategies, especially for treating hyperlipidemia and obesity, and other drugs are in development to treat cardiac disease and cancer and to improve cognitive function.

Mechanisms of thyroid hormone action

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Our understanding of thyroid hormone action has been substantially altered by recent clinical observations of thyroid signaling defects in syndromes of hormone resistance and in a broad range of conditions, including profound mental retardation, obesity, metabolic disorders, and a number of cancers. The mechanism of thyroid hormone action has been informed by these clinical observations as well as by animal models and has influenced the way we view the role of local ligand availability; tissue and cell-specific thyroid hormone transporters, corepressors, and coactivators; thyroid hormone receptor (TR) isoform–specific action; and cross-talk in metabolic regulation and neural development. In some cases, our new understanding has already been translated into therapeutic strategies, especially for treating hyperlipidemia and obesity, and other drugs are in development to treat cardiac disease and cancer and to improve cognitive function.

Introduction

Thyroid hormone regulates a wide range of genes after its activation from the prohormone, thyroxine (T4), to the active form, triiodothyronine (T3) (1). The signaling pathway is complex and highly regulated due to the expression of cell and tissue-specific thyroid hormone transporters, multiple thyroid hormone receptor (TR) isoforms, and interactions with corepressors and coactivators (2, 3). Furthermore, in many cases, thyroid signals are involved in cross-talk with a range of other signaling pathways (4, 5). Here, we review how clinical observations and animal models have shaped our understanding of this pathway, and how this insight might be translated to therapeutic approaches for a range of conditions (Table 1).

Overview of thyroid hormone action

Thyroid hormone is produced by the thyroid gland, which consists of follicles in which thyroid hormone is synthesized through iodination of tyrosine residues in the glycoprotein thyroglobulin (6, 7). Thyroid stimulating hormone (TSH), secreted by the anterior pituitary in response to feedback from circulating thyroid hormone, acts directly on the TSH receptor (TSH-R) expressed on the thyroid follicular cell basolateral membrane (8). TSH regulates iodide uptake mediated by the sodium/iodide symporter, followed by a series of steps necessary for normal thyroid hormone synthesis and secretion (9). Thyroid hormone is essential for normal development, growth, neural differentiation, and metabolic regulation in mammals (2, 3, 10) and is required for amphibian metamorphosis (11). These actions are most apparent in conditions of thyroid hormone deficiency during development, such as maternal iodine deficiency or untreated congenital hypothyroidism, manifesting as profound neurologic deficits and growth retardation (6). More subtle and reversible defects are present when ligand deficiency occurs in the adult (12).

There are two TR genes, *TR*α and *TR*β, with different patterns of expression in development and in adult tissues (2, 13). *TR*α has one T3-binding splice product, *TR*α*1*, predominantly expressed in brain, heart, and skeletal muscle, and two non–T3-binding splice products, *TR*α*2* and *TR*α*3*, with several additional truncated forms. *TR*β has three major T3-binding splice products: *TR*β*1* is expressed widely; *TR*β*2* is expressed primarily in the brain, retina, and inner ear; and *TR*β*3* is expressed in kidney, liver, and lung (2). Human genetics, animal models, and the use of selective pharmacologic agonists have been informative about the role and specificity of the two major isoforms (2, 14, 15). The selective actions of thyroid hormone receptors are influenced by local ligand availability (1, 16); by transport of thyroid hormone into the cell by monocarboxylate transporter 8 (MCT8) or other related transporters (17); by the relative expression and distribution of the TR isoforms (13) and nuclear receptor corepressors and coactivators (18); and, finally, by the sequence and location of the thyroid hormone response element (TRE; refs. 19, 20) (Figure 1). In addition, nongenomic actions of thyroid hormone, those actions not involving direct regulation of transcription by TR, have been increasingly recognized (21). Membrane receptors, consisting of specific integrin αv/β3 receptors, have been identified (22) and found to mediate actions at multiple sites, including blood vessels and the heart (23). Several studies have identified direct actions of TR on signal transduction systems (2, 24), which may be especially significant in relation to actions in cell proliferation and cancer.

The broad range of genes whose expression is modified by thyroid hormone status makes studying the effect of thyroid hormone action a daunting challenge (25). Many of the actions of thyroid hormone are the result of potentiation or augmentation of other signal transduction pathways (Table 2 and ref. 5). In metabolic regulation, this includes potentiation of adrenergic signaling (26–29) as well as direct interaction with metabolic-sensing nuclear receptors (30–32). Similar direct receptor-to-receptor interactions and competition for overlapping DNA response elements are seen in neural differentiation, as TR interacts with chicken ovalbumin upstream transcription factor 1 (COUP-TF1) and retinoic acid receptor (RAR) (3, 33).

TR isoforms differ in length at both amino and carboxy termini and are differentially expressed developmentally and spatially (Figure 1). The structure of *TR*α and *TR*β are similar in the DNA and ligand domains and differ most in the amino terminus, and it is thought that the increased potency of *TR*α is related to its amino terminus (34). Fundamental differences in the ligand-binding pocket have permitted the design of ligands that specifically interact with *TR*α or *TR*β (35), and these have been important tools in the dissection of isoform-specific actions.

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Table 1
Clinical observation influencing understanding of thyroid hormone action

Clinical condition	Mechanism	Key manifestations	Thyroid function studies	Treatment/reversibility	Reference
RTH	*TR*β heterozygous dominant-negative[A]	Variable, can include goiter; hearing deficit; hyperactive behavior; learning disability; developmental delay; tachycardia	Elevated serum T4 and T3; nonsuppressed TSH	No single treatment and should be individualized; high-dose T3 every other day can suppress TSH and reduce goiter; treatment to reduce T4 may be indicated during pregnancy to reduce miscarriage rate; other targeted treatment based on symptoms[B]	63, 64, 85
Severe-phenotype RTH	*TR*β homozygous dominant-negative mutation	Large goiter; dysmorphic features; severe tachycardia; developmental and growth delay; mental retardation; hearing deficit	Elevated serum T4[C]; elevated serum T3[D]; TSH, 35–490 mU/l[E]	Developmental defects not likely to be reversible; cardiac protection with β-adrenergic blockers; optimal thyroid hormone levels not known	70
RTH variant from *TR*α mutations	*TR*α heterozygous dominant-negative mutation	Short stature; delayed bone development; transient delay in motor development; mild impairment of cognitive development; chronic constipation	Serum free T4 and rT3 in low-normal range; T3 in high-normal range; normal TSH	T4 treatment to normalize TSH improved growth and metabolic rate in a few patients studied	67, 68
Short stature, delayed bone age	*SECISBP2* mutation[F]	Short stature and delayed bone age; selenoprotein deficiency partial; only children studied, so phenotype into adulthood not known	Elevated serum T4; low serum T3 relative to elevated T4; elevated rT3; slightly elevated TSH	TSH suppressed with T4 or T3 treatment; benefit of selenium treatment not known	52, 64
Profound mental retardation, Allan-Herndon-Dudley syndrome	*MCT8* mutation	Profound developmental delay; truncal hypotonia and poor head control; mental retardation; spasticity	Elevated serum T3; low serum T4 and rT3; TSH normal or slightly elevated	DITPA does not require MCT8 to reach brain, but likely needs to be given at an early developmental stage for benefit	54, 55
Linkage of D2 polymorphisms to obesity and type 2 diabetes	Reduced D2 activity; less local production or activation of T3 from T4	Subtle reduction in local T3; perhaps some reduction in resting energy expenditure	Normal serum levels of T4, T3, and TSH	May respond to treatment with T3; challenge is how to monitor and follow when trying to normalize local T3 levels	45, 46

[A]*TR*β gene homozygous deletion in initial family (63), 15% of which displayed no TR mutation. [B]For example, β-blocker for tachycardia. [C]3- to 6-fold upper limit normal. [D]7- to 10-fold upper limit normal. [E]Reference range, 0.3–4.5. mU/l. [F]Mutation mediates insertion of selenocysteine into selenoproteins.

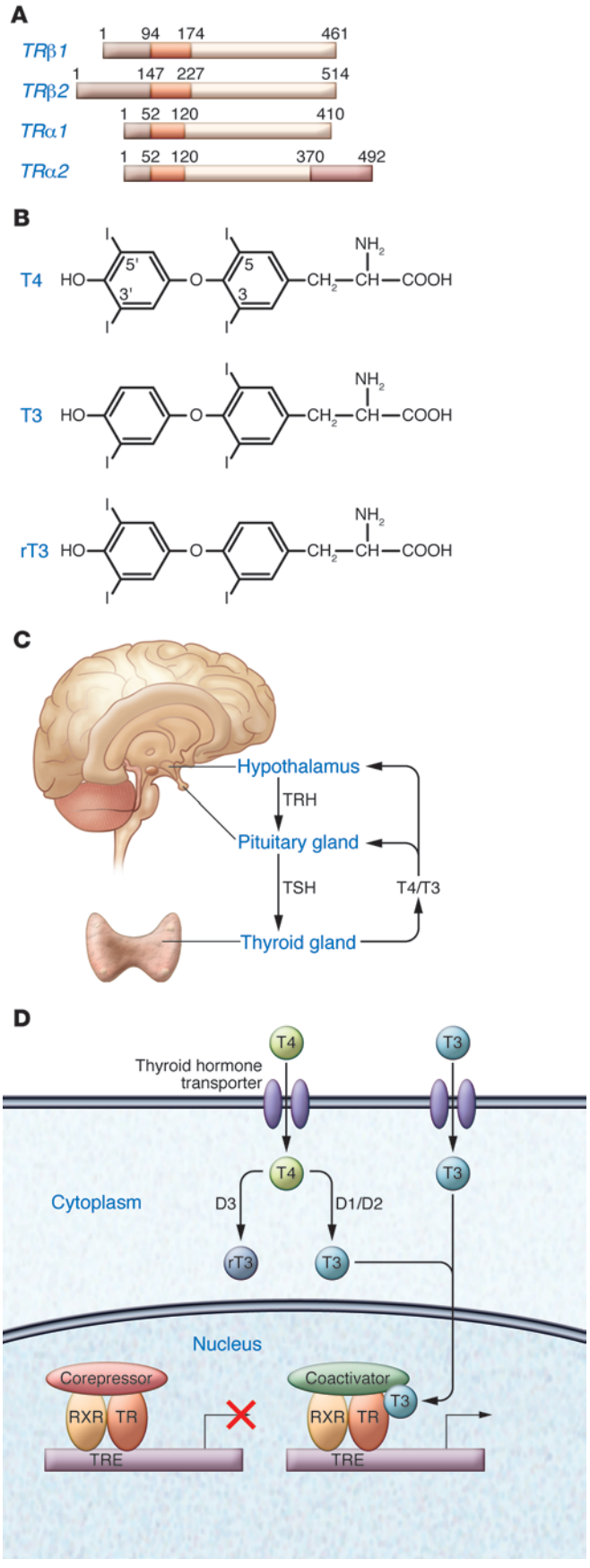

Figure 1
Nuclear action of thyroid hormone. Shown are the key components required for thyroid hormone action, as demonstrated by a range of clinical observations. (**A**) The TR gene has 2 major isoforms, *TR*β and *TR*α; the structures of *TR*α*1* and *TR*α*2* (non–T3-binding) and *TR*β*1* and *TR*β*2* are shown. (**B**) The major thyroid hormone forms, T4, T3, and rT3. (**C**) Circulating T4 is converted locally in some tissues by membrane-bound D2 to the active form, T3. D3 converts T3 to the inactive rT3. (**D**) In specific tissues, such as brain, transporters such as MCT8 transport T4 and T3 into the cell. Unliganded TR heterodimerizes with RXR and binds to a TRE and then to a corepressor, such as NCoR or SMRT, repressing gene expression. T3 binding to the ligand-binding domain results in movement of the carboxyterminal helix 12, disruption of corepressor binding, and promotion of coactivator binding, which then leads to recruitment of polymerase III and initiation of gene transcription.

TR isoform selectivity for TRE sequences in genes that mediate thyroid hormone response have been seen in some studies, but not all. TRE sequences influence TR isoform interaction with ligand (36) and may influence coactivator recruitment (37). TR interaction with TREs is not static; as has been reported with other nuclear receptors, there is variation in the pattern of binding that may be influenced by the TRE (37). In vitro studies have shown some TR isoform preferences for specific TREs (38), although the ability to translate these findings to in vivo observations are likely limited. Liver gene profiling in *TR*α and *TR*β gene knockouts demonstrates little in the way of specific genes linked to a TR isoform (25). A recent study, however, suggests that the relative potency of activation may be controlled more by the relative expression of *TR*α or *TR*β in a tissue, rather than by TR isoform specificity for a specific TRE (39).

Cell membrane thyroid hormone transport and local ligand availability

Local activation of T3 from the prohormone T4 at the tissue level is increasingly recognized as an important mechanism of regulation of thyroid hormone action (40). The activity of type 2 5′-deiodinase (D2) is regulated by a ubiquitinase/deubiquitinase mechanism. T4 deiodination by D2 results in exposed lysine residues in D2: ubiquitination of these residues reduces D2 activity, and deubiquitination increases D2 activity (41, 42). Rodents derive circulating T3 primarily by the action of type 1 5′-deiodinase (D1), but humans rely primarily on D2 (1). The inactivation of T4 to form reverse T3 (rT3), mediated by type 3 5-deiodinase (D3), is also important in regulating tissues levels of T3, especially in thyroid axis regulation and sensory development (43, 44). Some — but not all — human genetic linkage studies of polymorphisms in *D2* have shown an association with obesity and diabetes (45, 46).

The relationship between the level of serum T4 and serum TSH, termed the *set point*, is stable for an individual when repeatedly measured prospectively, but varies significantly between individuals (47). This variability in set point in the population suggests that there is a genetic influence involving one or more genes in the thyroid hormone pathway (48). D2 polymorphisms have been associated with an altered pituitary set point of TSH (49) and with a blunted increase in serum T4 after thyrotropin-releasing hormone–stimulated (TRH-stimulated) acute increase in serum TSH (50). Specific D2 polymorphisms were linked to an improved response in hypothyroid patients to replacement with combined therapy of T4 and T3, rather than T4 alone (51). These

Table 2
Thyroid signaling cross-talk with other pathways from in vitro and in vivo models and TR isoform preference

Pathway/nuclear factor or target	Process or tissue	TR isoform	Nature of interaction	Reference
RAR	Neural development	TRα1	Inhibits T3 action generally by direct inhibition of TR	96–98
Retinoic acid	Brain development	TRα1	Stimulates MCT8 expression and thyroid transport	103
COUP-TF1	Expressed early in brain development	TRα1	Blocks TR binding to a TRE and inhibits T3 induction of gene expression	99, 100
PPARα	Liver	TRα1	Fatty acid oxidation	26
PPARγ	Liver	TRβ	Lipid homeostasis	110
LXRα	Liver	TRβ	Cholesterol metabolism	111
LXR	Brain	TRα1	Cortical layering	113
p85α subunit of PI3K	Thyroid and liver	TRβ[A]	Cell proliferation; tumorigenesis	24, 130
β-Catenin	T3 stimulates expression in intestinal epithelium	TRα1	Proliferation; tumorigenesis	133
Adrenergic signaling	White fat	TRα1	Promotes lipolysis	30
Adrenergic signaling	Brown fat	TRα1[B]	Adaptive thermogenesis	27–29
Adrenergic signaling	Heart	TRα1	Tachycardia	30
Adrenergic signaling	Bone	TRα1[C]	Increased bone turnover and bone loss	89, 135

[A]Wild type and mutant. [B]TRβ regulates UCP1. [C]Role also for TRβ.

patients may have reduced conversion of T4 to T3 at the tissue level and benefit from replacement with T3. Selenium is required for the enzyme function of all three deiodinases. Individuals with abnormal thyroid hormone metabolism have been described with defects in the *SECISBP2* gene, which is required for the synthesis of selenoproteins (52), thus confirming the essential role of this mineral in thyroid metabolism (Table 1).

Thyroid hormone is hydrophobic and was long thought to enter into the cytoplasm by passive diffusion. Thyroid hormone transporters, such as the monocarboxylate (MCT) family and organic anion transporters (OATPs), were identified based on measurable in vitro activity, but the physiologic significance of these transporters was not established early on (17). MCT8 was identified as a specific transporter of thyroid hormone and was reported to be located on the X chromosome (53). Individuals with a severe form of X-linked mental retardation, Allan-Herndon-Dudley syndrome, manifest with truncal hypotonia, poor head control, and later spasticity and were found to have abnormal thyroid function (elevated serum T4 and rT3 and low T3). When *MCT8* was sequenced in these patients, inactivating mutations were identified in some individuals (54, 55). More recently, a mouse model with MCT8 inactivation demonstrated that MCT8 is also important for secretion of thyroid hormone (56). Oatp1c1 was shown in a mouse model to be important for thyroid transport across the choroid plexus and into the brain (57).

Thyroid transporters in the developing brain are expressed in specific temporal and spatial patterns (17, 58). Individuals with an *MCT8* mutation have myelination delays, which are thought to be caused by impaired thyroid hormone action on oligodendrocytes (59). MCT8 is expressed in the hypothalamus, a major site of integration of thyroid hormone feedback and gene regulation (60). Exogenous T3, even in the presence of functional MCT8 transporters, does not act on fetal rat brain, due to the requirement for local production of T3 from T4 (61). Studies of MCT8 have shown that the thyroid hormone metabolite diiodothyropropionic acid (DITPA) does not require MCT8 to enter into cells and is a potential therapy for those affected by MCT8 mutations (62). It is likely, however, that DITPA therapy will require treatment at an early stage of brain development to be effective. Thus, thyroid hormone action in the brain is modulated by both regional activation and selective uptake into cells, identifying multiple selective targets for therapeutic interventions.

Expanded spectrum of resistance to thyroid hormone: *TR*α and *TR*β gene mutations

The major clinical condition associated with impaired nuclear action of thyroid hormone, resistance to thyroid hormone (RTH), was first described in 1967 (63). Clinical features include goiter, elevated circulating thyroid hormone levels, nonsuppressed serum TSH level, clinical euthyroidism, and tachycardia; some individuals also demonstrate attention deficit disorder and deficits of linear growth, hearing, and bone formation (64). The RTH genetic defect was firmly established by a report published more than twenty years ago of a *TR*β mutation in an RTH kindred (65).

The potential phenotype of a *TR*α mutant RTH syndrome was considered based on the phenotype in animal models with *TR*α deletion or mutation (66). Recently, two families with different inactivating point mutations in *TR*α that resulted in receptors with dominant-negative properties have been reported (67, 68). The individual with an E403X *TR*α mutation had chronic constipation, developmental delay, and short stature, with some improvement after levothyroxine therapy (67). The index patient and her father — who was found to have an insertion of thymine at codon 397 of *TR*α, resulting in a frameshift and stop codon at 406 — had short stature, delayed bone development, transient delay in motor development, and mildly impaired cognitive development; they also had some improvement with T4 treatment (68). Levels of free T4 and rT3 in these patients were in the low-normal range, and T3 in the high-normal range, with normal TSH. These reports are a long-awaited complement to the well-characterized *TR*β mutations and provide very strong support to the results of genetic and pharmacologic studies indicating that TR isoforms have distinct roles.

It is of particular interest to compare the phenotype of *TR*α and *TR*β mutations in humans and determine the in vivo role of TR isoform specificity. An important difference is that *TR*β mediates thyroid hormone feedback to TRH/TSH, and a mutation blunts this feedback, such that more thyroid hormone is produced (8). In a limited study of RTH patients, the reduction in T3 affinity of the *TR*β mutant correlated with the slope of the serum TSH to serum T4 (69). The higher concentration of T4 and T3 in individuals with a *TR*β mutation may compensate for the impaired receptor signaling. In patients with *TR*α mutations, thyroid hormone feedback is not impaired to the same extent, so thyroid hormone levels are not elevated. This may result in peripheral hypothyroidism, and also points to a potential benefit of levothyroxine therapy in these individuals.

Recently, a report of several patients that are homozygous for *TR*β mutations demonstrated phenotypic features that represented a combination of those found in individuals heterozygous for a mutation only in *TR*α or in *TR*β (70). Patients homozygous for *TR*β mutations have a more severe phenotype of RTH — goiter, hearing loss, and much greater elevations of serum T3, T3, and TSH — than heterozygous individuals. Those homozygous for a *TR*β mutation also have intellectual deficits and growth retardation, more characteristic of deficient action of *TR*α (67, 68). This shows that the mutant *TR*β, expressed at sufficiently high levels, antagonizes the actions of *TR*α.

Role of TR interaction with cofactors

The essential function of gene repression by transcription factor corepressors in development and homeostasis is being increasingly recognized (71, 72). Initial in vitro transfection studies with TR expression vectors showed that the unliganded receptor had a repressive effect on genes positively regulated by T3 and an activating effect on genes normally repressed by T3 (73). The significance of this property has subsequently been demonstrated by several in vivo models. The mouse model with complete absence of *TR*α and *TR*β has a milder phenotype than a hypothyroid mouse (74). In the setting of *TR*α gene deletion, the structural effects of induced neonatal hypothyroidism on the mouse brain were not seen (75). The repressive actions of the unliganded receptor, therefore, have a greater physiologic effect than having no receptor at all (18). The interaction of TR with corepressors has been carefully mapped and tested (76, 77). Astapova et al. recently described a mouse model that expressed a version of nuclear receptor corepressor (NCoR) with a mutation in the region that binds TR (78). The disruption of this interaction resulted in a blunted TSH response to thyroid hormone, but enhanced peripheral tissue sensitivity, as the animals were euthyroid despite lower circulating thyroid hormone levels. Interestingly, a mutant NCoR ubiquitously expressed in the background of a *TR*β RTH mutant reversed much of the resistance phenotype seen in that model (79). This indicates that constitutive TR interaction with a corepressor is an important mechanism for RTH.

In a similar approach, mutation of the coactivator interacting domain in TRβ resulted in resistance to the action of thyroid hormone (80). The interaction of NCoR with histone deacetylase 3 seems to be important for both T3-induced gene activation and repression (81). Another approach to determine the importance of TR coactivator interactions is to determine the impact of coactivator knockouts on thyroid hormone action (82, 83). Mice deficient in the coactivator SRC1 showed increased resistance to the action of thyroid hormone (84). These models may provide a mechanistic basis for the approximately 15% of individuals with an RTH phenotype who lack mutations in *TR*β, although no cofactor gene mutations have yet been identified in these patients (85).

TR isoforms and neural development

Highly selective TR isoform requirements have been shown most clearly in models of sensory development, with marked and selective defects of structure and function in the setting of TR isoform inactivation (86). These include development of the inner ear and the cone photoreceptors in the retina (87, 88). Another site with specific TR isoform function is bone, both developmentally and in the adult (89). The developmental importance of TR isoforms is coupled with a requirement for specific transporter expression, such as MCT8 expression in the mouse cochlea (58), as well as a requirement for D2 expression to provide local T3, and for D3 to inactivate thyroid hormone and protect from excessive T3 action during sensitive periods (86, 90).

Thyroid hormone interfaces with other signaling pathways in neural development (Table 2). There is a close developmental link between retinoic acid action in early neurologic development and thyroid hormone action (3). In most model systems studied, retinoic acid acts first, followed by thyroid hormone action. Several studies have shown thyroid hormone targets in early neurological development and a requirement for TRα expression (91, 92). There are multiple genes whose expression is known to be regulated by both TR and RAR at the TRE (93–95). TR and RAR interact in promoting neural differentiation (96, 97), including a repressive action of the unliganded RAR, as has been shown for unliganded TR (73, 98).

The orphan nuclear receptor COUP-TF1 is expressed early in neurological development, when thyroid hormone is present, but before the brain is responsive to it (33). Thyroid hormone responsiveness of the brain is associated with reduced expression of COUP-TF1. Numerous thyroid hormone gene targets have been identified with overlapping TR and COUP-TF1 response elements (99, 100). The expression of COUP-TF1 blocks TR from binding the TRE, consistent with protection from early T3 stimulation. Calcium calmodulin–dependent kinase IV (CamKIV), a major thyroid hormone target gene in the developing brain, contains a TRE and COUP-TF1 binding site (101). CamKIV is regulated directly by T3 in primary cultured neurons from fetal cortex and promotes the maturation and proliferation of GABAergic interneurons from their precursor cells (102). The timing of the transport of thyroid hormone is tied to RA based on the stimulation of *MCT8* gene expression. Using a neuronal cell model, RA was shown to stimulate *MCT8* mRNA expression and to confer thyroid hormone transport (103).

TRα protein is expressed in embryonic postmitotic neurons and most adult neurons in the mouse brain, which suggests that thyroid hormone may also have a significant role in the adult brain (104). Thyroid hormone acting through TRα regulates adult hippocampal neurogenesis, which is important in learning, memory, and mood (105, 106). Expression of a mutant TRα is associated with more depressive behavior traits in mice (107).

TR isoforms and metabolic regulation

Specific actions of TR isoforms have been demonstrated for metabolic regulation, including in white fat and brown adipose tissue (BAT). TRα potentiates adrenergic action in white fat, and when *TR*α is mutated, visceral fat accumulates (30). BAT expresses both TRα and TRβ, which have selective roles in adaptive thermogenesis (28, 29). Adaptive thermogenesis requires adrenergic stimula-

tion, T3, D2, uncoupling protein 1 (UCP1), and both TRα and TRβ (27). The TRα isoform is required for adrenergic signaling (30), and the TRβ isoform is required for stimulation of UCP1 (29). In addition to these examples of thyroid hormone potentiation of peripheral adrenergic signaling, thyroid also influences adrenergic signaling centrally (108).

RTH patients with dominant-negative *TR*β mutations have some growth retardation and skeletal defects, but do not consistently present with metabolic abnormalities. However, in a recent study of RTH patients, increased resting energy expenditure was reported (109). These findings suggest that TRα actions mediating adrenergic sensitivity and fatty acid oxidation may be activated by the higher thyroid hormone levels in RTH patients, as is seen in the heart (5).

TRs engage in cross-talk with a range of nuclear metabolic receptors, including PPARα (26), PPARγ (110), and liver X receptor (LXR), in metabolic regulation (111, 112) and in brain cortical layering (Table 2 and ref. 113). The role of thyroid hormone receptor as an endocrine modulator of metabolic regulation, interacting with other nuclear receptors, PPARγ coactivator 1 (PGC-1), and p160 coactivators and corepressors, has been well described (114).

Our understanding of metabolic cross-talk has been applied directly to therapy with the use of TRβ agonists for lipid lowering and weight loss (15, 115). TRβ agonists have approximately 10-fold greater affinity for TRβ than TRα. Initial studies with TRβ agonists showed a marked preference for action in the liver, efficacy in lowering of cholesterol, and, for some compounds, weight loss, all with little effect on heart or bone. A phase 2 trial of the TRβ agonist eprotirome in patients who had not reached LDL target level with a statin demonstrated that the addition of eprotirome produced a dramatic improvement in LDL (116), although cartilage damage in longer-term dog models has led to the withdrawal of these compounds from clinical trials. Although these actions speak strongly for TR isoform specificity, a significant part of the specificity of action of these agents is much greater concentration of the selective agonist compound in the liver compared with the heart (117). A recent study found that the changes in gene expression in the liver were the same after T3 stimulation or exposure to the selective TRβ agonist GC1 (118). MB07811 achieves liver specificity by being activated after entering hepatocytes by the action of cytochrome P450 to generate the TRβ agonist MB07344 (119). Interestingly, providing hypothyroid human subjects with only T3 rather than T4, but keeping their TSH in the normal reference range, also results in reduced LDL cholesterol and slight weight loss (120). This modest local hepatic excess of T3 may be sufficient to lower cholesterol and produce weight loss, even when systemic levels are in the normal range.

The thyroid hormone analog DIPTA was found to have some specificity for action on the heart and was studied in a prospective randomized control study in patients with severe heart failure (121). Although improvement in some cardiac parameters was seen, the metabolic effects of weight loss were profound, and the study stopped. The metabolic effects of DITPA — reduction in body weight and LDL cholesterol — provide encouragement for beneficial effects of this class of compound, although stimulation of bone turnover and bone loss by DITPA will limit its therapeutic use (122).

The clinical utility of a TR antagonist has been considered primarily to antagonize the cardiac effects of thyroid hormone, such as ischemia and arrhythmias (123). The structure of the apo TR, without ligand, has not been solved, but important features have been identified from studies of the liganded receptor with agonists and antagonists (35, 123). Helix 12 is the carboxyterminal helix of TR, which folds in response to ligand and is essential for TR interaction with coactivators and corepressors (124). TR antagonists have been designed by adding extension groups on TR agonists that interfere with Helix 12 folding (123), although this approach is not specific for TRα or TRβ.

Association of thyroid hormone receptor mutations with cancer

The viral oncogenes v-erbA and v-erbB are the mediators of avian erythroblastosis retrovirus (AEV) induction of erythroleukemias and fibrosarcomas in chickens, first recognized in 1935 (125–127). v-erbA was later recognized as a mutant version of TRα, with features that favor oncogenic activity, including deletion of the Helix 12 TR domain, which prevents T3 binding.

The link between the origins of TR and oncogenes is consistent with the role of thyroid hormone signaling and mutant TRs in several forms of cancer. The PV model, in which animals harbor a specific truncation of *TR*β, is associated with the development of thyroid cancer (128). In related studies, *TR*β mutations have been identified in a range of cancers, including hepatocellular carcinoma, renal cell carcinoma, erythroleukemias, and thyroid cancer (127, 129). TSH-secreting pituitary tumors have also been linked to *TR*β mutations. *TR*β mutants are associated with direct interaction with the regulatory p85α subunit of PI3K, which leads to activation of PI3K and increased phosphorylation of Akt and mTOR and results in cellular proliferation and migration (24, 130). Mutations in *TR*β promote metastatic spread of thyroid cancer (131). *TR*β mutants have also been linked to pituitary tumors by activation of the cyclin D1/cyclin-dependent kinase/retinoblastoma/E2F pathway (132). TRα directly stimulates transcription of the β-*catenin* gene in intestinal epithelial cells and may play a role in tumorigenesis in that tissue (133). Expression of D3, which inactivates thyroid hormone, has been associated with proliferation of malignant keratinocytes in basal cell skin carcinomas (134).

Summary

The elements required for thyroid hormone action are well recognized, but the interaction among the various pathways has been challenging to understand. Thyroid hormone interacts with a wide variety of signaling pathways, and its action is modulated based on nutritional and iodine status. A range of conditions with disordered thyroid signaling has allowed us to identify key regulatory pathways that are potential therapeutic targets. The availability of TR isoform–selective agonists and the recent reports of patients with RTH due to *TR*α mutations, as well as those homozygous for *TR*β mutations, are strong evidence for TR isoform specificity. The role of the pituitary in responding to a defect in a thyroid hormone action pathway is central to the resulting phenotype. These pathways, as well as the role of thyroid hormone in metabolism, cardiac function, and oncogenesis, are likely to be the focus in applying these findings.

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