Thyroid hormone and thyroid hormone nuclear receptors: History and present state of art

Julius BRŤKO

*Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
E-mail: julius.brtko@savba.sk*

The present review traces the road leading to discovery of L-thyroxine, thyroid hormone (3,5,3'-triiodo-L-thyronine, T_3) and its cognate nuclear receptors. Thyroid hormone is a pleiotropic regulator of growth, differentiation, and tissue homeostasis in higher organisms. The major site of the thyroid hormone action is predominantly a cell nucleus. T_3 specific binding sites in the cell nuclei have opened a new era in the field of the thyroid hormone receptors (TRs) discovery. T_3 actions are mediated by high affinity nuclear TRs, TR α and TR β , which function as T_3 -activated transcription factors playing an essential role as transcription-modulating proteins affecting the transcriptional responses in target genes. Discovery and characterization of nuclear retinoid X receptors (RXRs), which form with TRs a heterodimer RXR/TR, positioned RXRs at the epicenter of molecular endocrinology. Transcriptional control via nuclear RXR/TR heterodimer represents a direct action of thyroid hormone. T_3 plays a crucial role in the development of brain, it exerts significant effects on the cardiovascular system, skeletal muscle contractile function, bone development and growth, both female and male reproductive systems, and skin. It plays an important role in maintaining the hepatic, kidney and intestine homeostasis and in pancreas, it stimulates the beta-cell proliferation and survival. The TRs cross-talk with other signaling pathways intensifies the T_3 action at cellular level. The role of thyroid hormone in human cancers, acting via its cognate nuclear receptors, has not been fully elucidated yet. This review is aimed to describe the history of T_3 receptors, starting from discovery of T_3 binding sites in the cell nuclei to revelation of T_3 receptors as T_3 -inducible transcription factors in relation to T_3 action at cellular level. It also focuses on milestones of investigation, comprising RXR/TR dimerization, cross-talk between T_3 receptors, and other regulatory pathways within the cell and mainly on genomic action of T_3 . This review also focuses on novel directions of investigation on relationships between T_3 receptors and cancer. Based on the update of available literature and the author's experimental experience, it is devoted to clinicians and medical students.

Key words: thyroid hormone, nuclear thyroid hormone receptor, gene expression, thyroid hormone-inducible transcription factor, retinoid X receptor, molecular mechanism of action

The first indirect references regarding the thyroid gland, which are predominantly linked with its diseases, have appeared in the texts of Egyptian, Chinese and later also of ancient Greek medicine dating back to 2700 BC. Due to a goiter widespread prevalence in population, it has always been a disease of immense interest (Niazi et al. 2011). In

the 6th century, Aetius made the reference to the surgical treatment of goiter, which was considered to be a hernia of the larynx (Marketos et al. 1990). In 1656, an anatomist Thomas Wharton described the anatomical structure of the thyroid gland along with the other glands of the body. Moreover, he demonstrated that the primary function of thyroid gland

is secretion. In 1907, David Marine proved that an element iodine is necessary for thyroid function (Niazi et al. 2011).

In 1914, Edward Calvin Kendall underwent hydrolysis of the enormous amount of the bovine thyroid glands and he succeeded with the first isolation of crystalline thyroxine (Kendall 1915). Later on, thyroxine was prepared synthetically by condensation of two molecules of diiodotyrosine, which led to the description of the exact structure of thyroxine. (Harington and Barger 1927). A breakthrough in the thyroidology came with the discovery of Jack Gross and Rosalind Pitt-Rivers (1952) postulating that 3,5,3'-triiodo-L-thyronine (T_3) is the "true" peripheral thyroid hormone, while the L-thyroxine (T_4) is its precursor.

In the second half of the previous century, the radioligand binding assays, using the radioisotope iodine (^{125}I) with high specific activity, opened at least three decades of thoughtful investigation on thyroid hormone binding sites in the cell organelles in relation to mechanism of thyroid hormone action. Tabachnick et al. (1954) have demonstrated distribution of labelled thyroxine in rat liver homogenates and demonstrated only non-specific binding. Later, the binding of both radiolabeled compounds (T_4 and T_3) to mitochondria and microsomes isolated from rat liver and skeletal muscle (Tata et al. 1962), and also to soluble proteins of rat liver (Spaulding and Davis 1971) has been demonstrated.

From T_3 binding sites in nucleus to T_3 receptors

Even in 1967, Tata and his co-workers were the first who contemplated that thyroid hormone might be capable to initiate its action by stimulating gene transcription. Next year will be half a century since Oppenheimer and his colleagues (1972) brought the first strong evidence that nuclei from rat liver and kidney possess a set of receptor sites, which exhibit specificity for T_3 . These receptors exert high affinity and limited capacity to T_3 binding in nuclei. Specific binding of T_4 to nuclei was also confirmed, but it represented only the one-tenth of that exhibited by T_3 (Surks et al. 1973, 1975; Koerner et al. 1975). Consequently, a correlation between the affinity of the nuclear T_3 binding sites and the biological potency of thyroid hormone has been confirmed, as well (Koerner et al. 1975; Oppenheimer et al. 1976). The presence of specific nuclear T_3 binding sites – nuclear thyroid hormone receptors (TRs) in various tissues has been demonstrated by many independent groups of investigators (Oppenheimer et al. 1974; Samuels et

al. 1974; DeGroot and Torresani 1975; Eberhardt et al. 1978) and the support for T_3 mitochondrial receptors has been rather less forthcoming (Sterling et al. 1977; Naidoo et al. 1978). Nuclear TRs were found to be acidic non-histone chromatin proteins, easily extractable in high ionic strength solutions, what enabled investigators to employ further analyses to study their biological, biochemical, and physicochemical properties (Samuels et al. 1974; Surks et al. 1975; Torresani and DeGroot 1975; Barsano et al. 1990). The presence of TRs was also confirmed in cultured rat tumor pituitary GH_1 cells that were found to respond to T_3 with augmented growth hormone (GH) secretion (Samuels and Tsai 1973; Samuels et al. 1979). Rat liver nuclear TR was found to be rather unstable protein, which loses its T_3 binding activity at 0°C with a half-life of approximately 14 days or with a half-life of approximately 62 minutes at 36°C . The effect of glycerol on protection against loss of nuclear TR binding activity was clearly shown by heat-inactivation study and other *in vitro* analyses (Brtko et al. 1987, 1992a; Ichikawa et al. 1989). The TR was demonstrated to be unstable at a pH below 6.0 or above 10.0. Using a set of commercially available resins for purification of proteins (hydroxylapatite, Sephadex G-150, DNA-cellulose, DEAE-Sephadex A-150, heparin-sepharose), the protein fraction containing nuclear TR proteins has been purified to its relative value of the maximal binding capacity of 1220 pmol/mg protein with a final yield of 14.6 μg per 4 kg of rat liver (Ichikawa et al. 1989).

Protease inhibitors and substrates were found to inhibit steroid molecules binding to their cognate receptors (Baker et al. 1978; Hubbard and Kalimi 1985; Puca et al. 1986). These findings have been extended for TRs, showing that various protease inhibitors and protease substrates inhibit T_3 binding to nuclear TRs (Brtko et al. 1993).

The presence of saturable and high affinity T_3 binding sites was also demonstrated in nuclei of L1210 murine leukemia cells. Scatchard analysis revealed one class of nuclear receptors for T_3 with the $K_a=2.187\times10^9$ l/mol and the maximum binding capacity (B_{max}) of 3.96 fmol/ 10^6 cells, what represents 2385 T_3 receptor sites per nucleus (Brtko et al. 1992b). In L1210 murine leukemia cells, processes linked to T_3 receptor promotion in cell nuclei were effective within the late G_1 and S phases of the cell cycle, and thus the increase in T_3 receptor concentration in the nuclei was positively correlated with the number of cells in the S compartment of the cell cycle (Filipcik et al. 1992). The number of nuclear receptors for T_3 in the liver may be reduced by starvation,

glucagon treatment or partial hepatectomy (DeGroot et al. 1977a; Dillmann et al. 1978; Brtko and Knopp 1988). The most important property of the T_3 -nuclear receptor complex is its ability to stimulate transcription of target genes (DeGroot et al. 1977b; Glass and Holloway 1990; Brtko et al. 1994).

The data on the thyroid hormone binding to nuclei or nuclear proteins achieved during the second half of the previous century clearly demonstrate that the cell nucleus is the principal site for the initiation of thyroid hormone action (Oppenheimer 1999).

Nuclear T_3 receptors – T_3 -inducible transcription factors

A remarkable breakthrough in the field of nuclear TRs investigation came in the year 1986, with the discovery of two research groups showing that the *c-erbA* proto-oncogene, a cellular counterpart of the viral *v-erbA* oncogene, encodes a high affinity receptor for thyroid hormone. The laboratory of Björn Vennström succeeded in the cloning of the alpha form of thyroid hormone receptor (TR α), while the beta form of thyroid hormone (TR β) was accomplished in the laboratory of Ronald Evans (Weinberger et al. 1986; Sap et al. 1986; Thompson et al. 1987). Based on the above-mentioned reports, this breakthrough has triggered years of intense investigations on nuclear TRs, which significantly contributed to the identification of TR α 1, TR β 1 and TR β 2 receptors as thyroid hormone dependent transcription factors. In mammals, two distinct but closely related genes encode TRs. The human alpha- T_3 receptor gene has been localized to chromosome 17 (Thompson et al. 1987; Benbrook and Pfahl 1987; Koenig et al. 1988) and the human beta- T_3 receptor gene to chromosome 3, and it was reported to be tightly linked to the autosomal dominant syndrome of thyroid hormone resistance (Usala et al. 1988a; Glass and Holloway 1990).

TR α is ubiquitously expressed in vertebrates, however, TR β expression patterns were demonstrated predominantly in the liver, pituitary, inner ear, retina, and several brain areas (Flamant et al. 2006). The reports of Vennström's and Evans' groups markedly contributed to the discovery of "superfamily" of 48 genes present in the human genome, which comprises regulatory genes responsible for the coding nuclear receptors for glucocorticoids, mineralocorticoids, androgen, estrogen, progesterone, dihydroxyvitamin D_3 , all-*trans* and 9-*cis* retinoic acids and many other "orphan" nuclear receptors, for which the ligand still remains unknown (Giguere et

al. 1987; Evans 1988; Giguere et al. 1988; Green and Chambon 1988; Glass and Holloway 1990; Laudet et al. 1992).

All known nuclear receptors consist of a variable NH_2 -terminal domain (A/B), the domain C, which is a conserved DNA binding region, a linker region D, possessing a role as a hinge of the nuclear receptor molecule, and a conserved E domain that contains the ligand binding domain. Several nuclear receptors contain also a terminal F region containing a carboxyl group, the function of it still remains unknown (Evans 1988; Aranda and Pascual 2001). The domain C contains two "zinc fingers", which contain DNA recognition motifs forming with amino acids at the base of the first zinc finger the specific region known as „P-box“. The amino acid residues of the second zinc finger form the structure termed as "D box", which is involved in the nuclear receptor dimerization (Dahlman-Wright et al. 1993; Nelson et al. 1994; Zechel et al. 1994). The "P-box" is critical for identifying the primary nucleotide sequence of the half sites, while the "D-box" is important for the determination of the half-site spacing (Umesono and Evans 1989). Moreover, nuclear receptors contain two regions required for transcriptional activation, the hypervariable region located at the amino group end of the receptor molecule, which contains an autonomous transcriptional activation function, known as AF-1 that contributes to constitutive ligand independent activation by the nuclear receptor molecule. The second transcriptional activation domain, termed as AF-2, is located in the carboxyl group containing terminus of the nuclear receptor ligand binding domain. The transactivation domain AF-2 is strictly ligand dependent and conserved among members of the nuclear receptor superfamily (Baretino et al. 1994; Aranda and Pascual 2001).

TRs, similarly like other nuclear receptors, contain a variable N-terminal domain, a DNA binding domain followed by a hinge region, and a C-terminal ligand binding, dimerization, and transactivation domain. The TR α gene is transcribed as TR α 1 and TR α 2 mRNAs, which differ by alternative splicing of 39 exons, resulting in distinct C terminal domains. TR α 1 binds T_3 and DNA and is a functional T_3 receptor, whereas TR α 2 fails to bind T_3 and acts as a weak antagonist (Harvey and Williams 2002). The TR β gene is transcribed as TR β 1 and TR β 2 mRNAs, which are generated by separate promoter and alternative splicing in the 5' region resulting in distinct beta1 and beta2 protein N-termini (Williams 2000; Harvey and Williams 2002).

In 1990, the first identified nuclear retinoid X receptor (RXR), referred as RXRalpha, was initially described as an orphan receptor (Mangelsdorf et al. 1990). Two years later, three RXR genes (RXRalpha, RXRbeta, RXRgamma) were discovered and subsequently thoroughly characterized. In the same year, it has been demonstrated that retinoid X receptors (RXRs) interact with several nuclear receptors in signaling pathways mediated by all-*trans* retinoic acid (RA), thyroid hormone and vitamin D₃. In addition, 9-*cis* retinoic acid (9cRA) was confirmed to be a high affinity ligand for the RXR (Mangelsdorf et al. 1992; Kliewer et al. 1992; Heyman et al. 1992). Discovery and characterization of RXRs positioned them at the epicenter of the “Big Bang” of molecular endocrinology and gave rise to huge wave of novel discoveries, including new physiologic signaling pathways (Evans and Mangelsdorf 2014; Yamada and Kakuta 2014). RXRs perform their role as promiscuous dimerization partners for additional nuclear receptors, which act in a variety of nuclear receptor facilitated pathways (Germain et al. 2006a; Krezel et al. 2019; Brtko and Dvorak 2020). RXR molecules form permissive heterodimers with peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXR), farnesoid X receptor (FXR), pregnane X receptor (PXR) and constitutive androstane receptor (CAR). RXR/TR heterodimers are thought to be non-permissive for RXR, but several studies have suggested that there may be exceptions in specific cellular contexts (Castillo et al. 2004; Mengeling and Furlow 2015; Flamant 2016). Retinoid receptors (RARs) and TRs may form conditional heterodimers, and dihydroxyvitamin D₃ receptor (VDR) is at present believed to form nonpermissive heterodimer (Laudet 1997; Sanchez-Martinez et al. 2006; Yamada and Kakuta 2014; Brtko and Dvorak 2020).

Both types of TRs (TRalpha and TRbeta) are functionally active in the form of conditional heterodimer RXR/TR, which bind to thyroid hormone response elements (TREs) (Germain et al. 2006b; Brtko and Dvorak 2011). The TREs have been shown to consist of either the palindrome pair of hexameric (AGGTCA) “half-sites” or direct repeats of this sequence spaced by a “gap” containing preferentially four nucleotides (Glass et al. 1988; Wahlstrom et al. 1992). RXR molecule, as a part of heterodimer in a conditional heterodimer does not respond to retinoids, nevertheless, RXR agonists are capable to superactivate transcription of target genes by synergizing with the action of T₃ bound to TRs. Functional evidences on the role of RXR ligand in the RXR/TR heterodimer have already been demonstrated (Li et

al. 2002; Castillo et al. 2004; Brtko and Dvorak 2020). The interaction of the nuclear TRs with specific DNA sequences represents the crucial mechanism by which the transcription of target genes is controlled.

The discovery of coregulators (coactivators and corepressors) of nuclear receptors has greatly enhanced the understanding of TRs function. SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) and N-CoR (nuclear receptor corepressor) are two related transcriptional corepressors that contain separable domains capable of interacting with unliganded nuclear receptors and repressing basal transcription. The first reported functional nuclear receptor coactivator, termed the steroid receptor coactivator-1 (SRC-1), is considered to be a general coactivator for all steroid/thyroid subfamily of nuclear receptors and upon a ligand binding to cognate nuclear receptors, is responsible for the enhancement of transactivation of hormone-dependent target genes. In the other words, upon binding of the corresponding ligand, the nuclear receptors change their conformation in the ligand-binding domain that enables recruitment of coactivators, which allows the receptor to interact with the basal transcriptional machinery efficiently and to activate transcription of thyroid hormone-dependent genes (Horlein et al. 1995; Glass 1996; Shibata et al. 1997; Li et al. 1997). Among nuclear receptor coactivators also belong the transcriptional intermediary factor 2 (TIF2/GRIP-1/NCoA-2), the cAMP-response element binding protein (CREB)-binding protein (CBP), the p300/CBP-associated factor (p/CAF), the vitamin D receptor-interacting protein/TR-associated protein (DRIP/TRAP), and the mediator complex subunit 21 (MED/21), known as Srb7 (Nevado et al. 2004; Smith and O'Malley 2004; Rosenfeld et al. 2006; Giammanco et al. 2020).

The binding of T₃ to the TR molecule alters its conformation in such a way that the corepressor complex is replaced by a coactivator complex. The essential role played by SRC-1 in T₃ action mediated by TRs has been demonstrated by the finding that SRC-1 knockout mice exhibit thyroid hormone resistance in peripheral tissues as a major phenotype (Weiss et al. 1999). Coactivators p/CAF, p300, and SRC-1 possess histone acetylase activity and thus, modification of histones around the TRE promotes an open chromatin conformation allowing greater access for the basal transcriptional machinery (Harvey and Williams 2002). The thyroid hormone receptor activating proteins (TRAPs), T₃-dependent interacting factors, have been shown to play a similar role as interacting factors with vitamin D₃ receptor.

Protein p160 of the SRC family interacts with TR when T_3 binding occurs, but these proteins are subsequently replaced by the TRAP complexes to optimize transactivation (Ito and Roeder 2001; Harvey and Williams 2002). In general, T_3 -dependent transcriptional activity requires recruitment of both TRAP and p160 protein coactivator complexes to TR molecule. Protein p160 and TRAP coactivator complexes act in a sequential manner, p160 complexes act earlier than TRAP and this ordered recruitment may proceed for multiple cycles of association and dissociation, with multiple rounds of transcription occurring within each cycle (Metivier et al. 2006; Aranda et al. 2013).

Cross-talk of nuclear thyroid hormone receptors with other signaling pathways

Cross-talk between TRs and the second messenger pathways has also been previously demonstrated (Harvey and Williams 2002). Thyroid hormone action through their cognate nuclear receptors is potentiated by protein kinase A-dependent phosphorylation in a manner independent of the TRE structure, but dependent on the cell line studied (Leitman et al. 1996). Thyroid hormone antagonizes prolactin signaling during mammary gland development by the janus kinase 2 (JAK2)/signal transducer and activator of transcription 5 (STAT5) (Favre-Young et al. 2000; Harvey and Williams 2002). Also, a cross-talk between TR and LXR regulatory pathways has been demonstrated in a thyroid hormone resistance mouse model (Hashimoto et al. 2006). In addition, LXRalpha and TRbeta have been confirmed to exert their reciprocal cross-talk on ABCA1 gene promoter at the transcriptional level (Hashimoto and Mori 2010). Moreover, both TR and LXR are capable to interact with other nuclear receptors, as well (Xiao et al. 2010; Lu and Cheng 2010).

Cross-talk between the thyroid hormone signaling and regulatory pathways in cholesterol metabolism or metabolic pathways comprising fatty acid synthesis and beta-oxidation, has also been reported (Liu and Brent 2010).

Action of thyroid hormone via TRs on mammalian tissues

The genomic action of T_3 is based on the interactions with TRs and further binding to TREs of a variety of specific downstream genes. Thus, the transcriptional control via nuclear TRs represents the direct action of thyroid hormones (Glass and Holloway 1990; Liu et al. 2019).

In 1967, Refetoff was the first who demonstrated the resistance to thyroid hormones (RTH), which is characterized by reduced or impaired sensitivity of tissues to the actions of thyroid hormone. Later, it has been demonstrated that RTH syndrome is an autosomal dominant or recessive genetic disease caused by mutation of either nuclear receptor TRalpha or TRbeta (Refetoff et al. 2014; Tang et al. 2016; Sun et al. 2020). The RTH syndrome is normally inherited in autosomal dominant manner and is predominantly due to heterozygous mutations in TRbeta molecule (Chatterjee 1997; Refetoff and Dumitrescu 2007). Defects in any of the processes linked with thyroid hormone genomic actions give rise to distinct disease entities, collectively called thyroid hormone signaling disorders, and heterozygous mutations of TRbeta are the most common genetic cause of the RTH (Visser 2020). Mutations in TR molecule affecting the T_3 ligand binding domain interfere with T_3 binding to TR and have a dominant negative effect on the T_3 action, which means that TR molecules remain stably bound to the TREs in the repressive T_3 -free form, not allowing T_3 genomic action (Yen 2003; Giammanco et al. 2020).

The T_3 regulates the type 1 iodothyronine deiodinase mRNA in rat liver (Berry et al. 1990; Maia et al. 1995), which is one of the best-known thyroid hormone target genes (Koenig 2005; Flamant et al. 2006), and also increases type 2 iodothyronine deiodinase mRNA levels in rat brown adipocytes, the enzymes, which take part in the conversion of T_4 to T_3 (Martinez-deMena et al. 2002; Viguerie and Langin 2003). The T_3 plays a crucial role in the development of brain, acting on migration and differentiation of neural and glial cells, synaptogenesis, and myelination (Bernal and Nunez 1995; Bernal 2002, 2007). Hypothyroidism during the neonatal period of development causes mental retardation and a number of neurological defects (Viguerie and Langin 2003). TR isoforms, which are encoded by the TRalpha and TRbeta genes, are expressed in the brain, with the most common being TRalpha1 (Bernal 2007). In the cerebellum, TRalpha1 is predominantly expressed in the granular cell layer, whereas Purkinje cells predominantly express TRbeta1 (Morte et al. 2002; Bernal 2007). In the rat developing brain, the early phase of synaptogenesis is associated with a T_3 dependent expression of tubulin and actin (Poddar et al. 1996). Later on, it has been reported that T_3 regulates tubulin expression in mammalian liver, as well (Vallejo et al. 2005). T_3 was also found to regulate adult hippocampal neurogenesis, a process involved in functions such as learning, memory, and mood

regulation (Desouza et al. 2005; Montero-Pedrazuela et al. 2006; Pascual and Aranda 2013).

The T_3 exerts significant effects on the cardiovascular systems and plays an important role in cardiac development, function and the maintenance of a normal cardiac physiology (Dillmann 2002; Kahaly and Dillmann 2005). Alterations in the thyroid status markedly affect cardiac contractile and electrical activity. T_3 has a strong positive effect on the speed and force of the systolic contraction and the effect on the duration of diastolic relaxation in the heart (Mintz et al. 1991). T_3 affects the cardiac action by exerting a direct effect on cardiac myocytes through binding to nuclear TRs. A higher number of nuclear TRs was demonstrated in cardiac myocytes in comparison with cardiac fibroblasts that contain about one tenth of TRs present in cardiac myocytes (Dillmann 2002). Multiple thyroid hormone effects are mediated by both TRalpha and TRbeta, whereas the TRalpha was demonstrated to be the predominant isoform in the heart. Hypothyroidism is distinguished by systolic and diastolic dysfunctions with reduced force and slowed relaxation, whereas hyperthyroidism causes augmenting heart rate and producing tachycardia (Dillmann 2010; Pascual and Aranda 2013). Actually, an impact of altered thyroid status on both the occurrence and recurrence of cardiac arrhythmias, predominantly atrial fibrillation, has been recently summarized (Tribulova et al. 2020). Cardiac myosin heavy chains are under control of T_3 , which stimulates expression of the alpha-myosin heavy chain gene and inhibits beta-myosin heavy chain mRNA production both *in vivo* and in cultured heart cells (Gustafson et al. 1987; Morkin et al. 1991, 1993). In mammals, T_3 via TRs regulates the cardiac beta-adrenergic receptor-adenylate cyclase system by controlling the rate of transcription of the beta1-adrenergic receptor gene in a tissue-specific manner (Bahouth 1991), predominantly during a critical development period (Metz et al. 1996).

Skeletal muscle contractile function and myogenesis are affected by T_3 through TRalpha and TRbeta, but TRalpha appears to represent the major isoform mediating the effect of thyroid hormone. T_3 stimulates skeletal muscle growth by increasing number and diameter of the muscle fibers (Sugie and Verity 1985; Bloise et al. 2018).

The T_3 is essential for the bone development and growth. In adults, the bone mass maintenance is also under the control of thyroid hormone and physiological role of the thyroid hormone-activating enzyme type 2 iodothyronine deiodinase in the optimization of bone mineralization and strength has been

demonstrated (Waung et al. 2012; Lademann et al. 2020). The thyroid hormone controls skeletal development and growth, moreover, T_3 plays a role in adult bone mineralization, as well. TRalpha1 and TRbeta1 isoforms are expressed in bone tissue, although TRalpha1 is expressed at much higher concentration than TRbeta1, and in bone, TRalpha1 is considered to be a predominant mediator of thyroid hormone action (Freitas et al. 2005; Beber et al. 2009). Both TRalpha1 and TRbeta1 are expressed in chondrocytes, bone marrow stromal cells, osteoblasts, osteocytes, and osteoclasts (Gogakos et al. 2010; Pascual and Aranda 2013).

The T_3 acting via its cognate receptors is indispensable for the proper functioning of the female reproductive system, since it modulates the metabolism and development of ovarian, uterine, and placental tissues (Evans et al. 1983; Maruo et al. 1992; James et al. 2007; Silva et al. 2018). Thyroid dysfunction is associated with several physiological and behavioral alterations, comprising reproductive disorders in women (Choksi et al. 2003). Nuclear TR isoforms, TRalpha1 and TRbeta1, are present in the placenta, and their expression increases with fetal age (Chan and Kilby 2000; Silva et al. 2018).

The T_3 produces profound effects through its cognate receptors on the developing testis, affecting spermatogenesis, steroidogenesis, testis size, reproductive hormones and fertility. T_3 acts on testis in multiple ways and exerts its effect on different cell types, including Leydig and Sertoli cells and germ cells (Hernandez 2018; La Vignera and Vita 2018; Hernandez and Martinez 2020).

The T_3 plays an important role in maintaining the hepatic homeostasis. The first evidence that nuclei from rat liver possess a set of receptor sites, which exhibit specificity for T_3 was demonstrated nearly a half of the century ago (Oppenheimer et al. 1972). Liver tissue expresses both TRalpha and TRbeta, and in adult liver, TRbeta is the predominant isoform (Flores-Morales et al. 2002; Yen et al. 2003; Ritter et al. 2020), which plays a key role in liver cell proliferation (Pascual and Aranda 2013). Thyroid hormone affects the intermediary metabolism and it influences the transcriptional and posttranscriptional regulation of rat hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) (Simonet and Ness 1988). Also, the effect of T_3 on the chromatin structure and expression of the malic enzyme gene in hepatocytes has been confirmed (Usala et al. 1988b; Petty et al. 1989; Yin et al. 2005). Microarray analyses identified many novel gene candidates responsive to T_3 in liver affecting lipid metabolism, apoptosis and inflamma-

tory responses (Flores-Morales et al. 2002; Yen et al. 2003; Viguerie and Langin 2003; Flamant et al. 2006).

The T_3 influences renal development, kidney hemodynamics, glomerular filtration rate, and sodium and water homeostasis (Iglesias et al. 2017) and affects a variety of co-transport systems in the renal tubule, including the Na-P co-transporter, Na^+/H^+ exchanger, and the Na^+/K^+ ATPase in proximal convoluted tubule (Basu and Mohapatra 2012). Thyroid hormone has also been reported to affect the expression of atrial natriuretic factor at both the mRNA and the protein level in hypothyroid, euthyroid, and hyperthyroid rats (Ladenson et al. 1988), and is capable to induce Na^+/K^+ ATPases and sarcoplasmic Ca^{2+} -ATPases gene expression in a tissue-dependent manner (Gick et al. 1988; Gick and Ismail-Beigi 1990; Viguerie and Langin 2003).

In pancreas, the T_3 stimulates beta-cell proliferation and survival (Verga Falzacappa et al. 2006). T_3 bound to TRalpha takes part in activation of the cyclin D1/cyclin-dependent kinase/retinoblastoma protein/E2F pathway, along with cell cycle progression and cell proliferation (Pascual and Aranda 2013).

The T_3 controls the intestinal development and homeostasis. In the intestinal epithelium, which is physiologically rapidly regenerated, the importance of the TRalpha1 receptor has been demonstrated, notably in controlling the postnatal intestinal maturation (Frau et al. 2017). Both TRalpha and TRbeta are expressed in intestinal epithelial cells, but proliferation of epithelial cells depends predominantly on the TRalpha1, which is involved in the regulation of cell cycle control genes and of the Wnt/beta-catenin pathway, playing a role as a key modulator of cell proliferation in the intestinal epithelium (Plateroti et al. 1999, 2001; Pascual and Aranda 2013).

The skin, among the other target organs, is markedly influenced by thyroid hormone, which is essential for skin homeostasis, and skin diseases are frequently associated with an altered thyroid status (Mancino et al. 2021). By binding of T_3 to their cognate nuclear TRs (TRalpha and TRbeta), T_3 regulates epidermal cell proliferation, differentiation, and homeostasis (Contreras-Jurado et al. 2011; Antonini et al. 2013; Pascual and Aranda 2013).

The T_3 is also known to cause a rapid increase in the translational activity of a specific mRNA coding for a protein designated “Spot 14” (Jump et al. 1984; Liaw and Towle 1984). Later on, the “Spot 14” has been shown to play a key role in the tissue-specific regulation of lipid metabolism. It is a 17-kDa protein expressed in lipogenic tissues and was postulated to play a role in thyroid hormone stimulation of lipo-

genesis (Cunningham et al. 1998; Campbell et al. 2003). Human “Spot 14” protein interacts physically and functionally with the nuclear TR and it acts as a positive or negative cofactor to regulate malic enzyme gene expression induced by T_3 (Chou et al. 2007). Expression of T_3 responsive “Spot 14” is enhanced during differentiation of human adipocytes and its expression is down-regulated in obese subjects (Ortega et al. 2010).

The constitutive 63 kDa keratin genes involved in the *Xenopus laevis* development belong to genes activated by T_3 (Mathisen and Miller 1989). T_3 stimulates growth hormone (GH) gene transcription in rat pituitary tumor cells at both the mRNA and the protein level (Glass et al. 1987; Brent et al. 1989; Norman et al. 1989). T_3 acts via its cognate receptors by forming a more active transcription complex, which stimulates the level of GH gene expression (Ye et al. 1988).

In spite of the fact that a number of data clearly confirm the genomic action of T_3 , many novel gene candidates, responsive to T_3 and acting via TRs, remain to be discovered and their role clarified.

Nuclear thyroid hormone receptors and cancer

A number of studies have demonstrated the presence of either qualitative alterations, representing mutations or quantitative changes in the expression of TR genes in different types of human neoplasias. Qualitative alterations on the TR gene represent gross chromosomal or minor mutations, comprising deletions, aberrant splicing or point mutations. Quantitative changes involve the data on increased or decreased rate of expression of TRalpha and TRbeta genes (Gonzalez-Sancho et al. 2003). In human thyroid papillary carcinoma, the expression levels of TRalpha mRNA and TRbeta mRNA were significantly lower when compared to normal human thyroid tissue (Puzianowska-Kuznicka et al. 2002). Our results support these findings, moreover, it has been reported that decreased expression levels of both TRalpha and TRbeta mRNA in human thyroid papillary carcinoma with co-existent autoimmune thyroiditis were seen when compared to thyroid papillary tumor tissue of patients without autoimmune thyroiditis (Macejova et al. 2019). Moreover, mutation on TRbeta molecule plays a critical role in thyroid cancer development, as well (Liu et al. 2019). Functional TRs have been previously demonstrated in both thyroid carcinoma tissues and different thyroid tumor cell lines (Schmutzler et al. 1988). Contrary, investigation on TRs by the EMSA method in both the human benign toxic adenomas

and benign cold nodules has shown a significant increase of TRs level in toxic adenomas when compared to normal thyroid tissue from the same patient (Brtko et al 2002).

Distribution of TRs during the cell cycle in mouse leukemia cells has been demonstrated. It has been shown that processes involving TRs promotion in cell nuclei are operative within the late G₁ and S phases of the cell cycle, and thus the increase in T₃ receptor concentration in the nuclei is in a positive correlation with the number of cells in the S compartment of the cell cycle (Filipcik et al. 1992). *In vitro* data, indicating connections between TRs and cell cycle regulators and oncogenes, suggest that both TRalpha and TRbeta may be involved in human cancer (Gonzalez-Sancho et al. 2003). In GH₄C₁ rat pituitary tumor cells, biological effects of thyroid hormone depending on TRs occupancy by T₃, have been demonstrated, as well (Filipcik et al. 1998).

Reduced expression of TRs in tumor tissue and/or alterations in TR genes are considered to be common events in human cancer and have been previously comprehensively reviewed (Aranda et al. 2009; Font-Diaz et al. 2020). Reduced expression, anomalous cellular localization, and/or alterations of the TRbeta gene occur in many types of human tumors (Aranda et al. 2009). It has been shown that TRbeta may function as a tumor suppressor in mouse models of metastatic follicular thyroid carcinoma (Zhu et al. 2010) or in mammary tumors (Guigon et al. 2011; Font-Diaz et al. 2020) and control tumor cell proliferation and cancer cell defense pathways. In breast cancer, the transcription of the pro-apoptotic Bcl-2-associated death promoter (Bad) gene and X-linked inhibitor of apoptosis (XIAP) gene are downregulated by T₃ (Liu et al. 2019). In normal breast tissue, TRalpha1 is expressed during the pubescent, pregnancy and weaning period, and TRbeta1 is primarily expressed during lactation (Anguiano et al. 2004). TRbeta1 is associated with T₃ metabolic activity, while TRalpha1 plays an important role in the cell differentiation and apoptosis (Yen 2001; Macejova et al. 2005). Both TR isoforms may also have an opposite role in breast cancer, whereas TRalpha expression is high and TRbeta expression is missing (Jerzak et al. 2015, 2018; Font-Diaz et al. 2020). Decreased TRbeta expression, due to silencing of the corresponding gene, has been found in human cancer, including breast, lung, and thyroid carcinoma (Joseph et al. 2007). On the other hand, the expression of the TRbeta gene could also be repressed via microRNAs regulatory mechanisms in papillary thyroid cancer (Jadzewski et al. 2011; Kim and Cheng 2013).

The thyroid hormones modulate the expression of specific microRNAs (miRNAs) and their mRNA targets in different cell types and organs, and miRNA regulation is involved in the effects of TRs on cell proliferation and cancer (Aranda 2021). TRbeta has been found to induce the transcription of miRNAs, miR-424 and miR503, which belong to the miR-16 family, known for their capacity to down-regulate proliferation, migration and invasion of cancer cells. Induction of these miRNAs mediates some of the antiproliferative and antimetastatic actions of T₃ (Ruiz-Llorente et al. 2014; Font-Diaz et al. 2020; Aranda 2021).

New directions in the field of TRs investigation include questions regarding the cancer progression pathways, which show considerable variability and complexity. At present, the T₃ acting via TRs has not yet been established as a critical risk or prognostic factor for cancer. Both TR isoforms, which are involved in various tumor types and stages of development support the hypothesis on possible dual role of TRs in human cancers, either as an oncogene or a tumor suppressor. Reduced TR isoforms expression and/or alterations in TR genes are common events in human cancer (Gonzalez-Sancho et al. 2003; Aranda et al. 2009; Liu et al. 2019). The demonstration of a tumor suppressor role for the TRbeta isoform opens new therapeutic perspectives for the antiproliferative, differentiation-promoting function of the TRbeta isoform and its native cognate ligand T₃ as well as for TRbeta isoform-selective novel biologically active T₃ analogs (Kohrle 2004). Several mechanisms involved in the antitumorigenic and antimetastatic effects of TRbeta have been reported. The T₃ induces cellular senescence in the liver, a mechanism that is believed to act as a first barrier against cellular transformation and tumor development (Collado and Serrano 2010), which is mediated by T₃ binding to TRbeta, and not to TRalpha (Zambrano et al. 2014; Font-Diaz et al. 2020). The detailed role of functional significance of T₃ and its cognate TRbeta in tumors as well as mechanisms of antitumorigenic and antimetastatic actions of the TRbeta in human cancers has yet to be elucidated.

Concluding remarks

The cell nucleus represents a major site of the thyroid hormone action. The thyroid hormone receptors belong to a group of known 48 human nuclear receptors, which are ligand-activated, transcription-modulating proteins affecting transcriptional responses in target genes.

The T_3 , via its cognate TRs, plays a crucial role in the development of brain, it modulates differentiation of neural and glial cells, synaptogenesis, and myelination. T_3 through TRs regulates adult hippocampal neurogenesis, a process involved in functions such as learning, memory, and mood regulation. The T_3 acts on the cardiovascular systems and via TRs plays an important role in cardiac development, function and the maintenance of the normal cardiac physiology. Skeletal muscle contractile function and myogenesis are affected by T_3 through TRs. The T_3 is essential for the bone development and growth. The T_3 bound to TRs controls skeletal development and growth and bone mineralization. The T_3 acting via its TRs is also essential for the proper functioning of the female and male reproductive system. T_3 bound to TRs plays an important role in maintaining the hepatic homeostasis, it regulates expression of iodothyronine deiodinase and affects the intermediary and lipid metabolism. The T_3 via its TRs influences the renal development and kidney homeostasis, intestinal development and homeostasis and also plays a role in the stimulation of beta-cell proliferation and survival in pancreas. The skin is also influenced by T_3 , which upon its

binding to TRs regulates the epidermal cell proliferation, differentiation, and homeostasis.

The canonical pathway of T_3 signaling via nuclear TRs is considered to be sufficient to explain the most of the pleiotropic effects of T_3 in physiology, however, a number of questions still remains to be answered (Flamant 2016). Among the number of unanswered questions is the report demonstrating that mutations in the C-terminal domain of the TR molecule, located far from the ligand-binding pocket, reduce the affinity for T_3 binding (Marimuthu et al. 2002; Flamant 2016). Allosteric properties of RXR/TR complexes might also be relevant for the forthcoming studies of thyroid hormone disruptors, as several of environment affecting chemicals are thought to be TR ligands (Giera et al. 2011; Flamant 2016). Many additional unanswered questions regarding the properties of TRs in T_3 action have been thoroughly reviewed by Frederic Flamant (2016).

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