Deiodinases: the balance of thyroid hormone

Type 1 iodothyronine deiodinase in human physiology and disease

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Abstract

Thyroid hormone is essential for the normal function of virtually all tissues. The iodothyronine deiodinases catalyze the removal of an iodine residue from the pro-hormone thyroxine (T4) molecule, thus producing either the active form triiodothyronine (T3; activation) or inactive metabolites (reverse T3; inactivation). Type I deiodinase (D1) catalyzes both reactions. Over the last years, several studies have attempted to understand the mechanisms of D1 function, underlying its effects on normal thyroid hormone metabolism and pathological processes. Although peripheral D1-generated T3 production contributes to a portion of plasma T3 in euthyroid state, pathologically increased thyroidal D1 activity seems to be the main cause of the elevated T3 concentrations observed in hyperthyroid patients. On the other hand, D1-deficient mouse models show that, in the absence of D1, inactive and lesser iodothyronines are excreted in feces with the loss of associated iodine, demonstrating the scavenging function for D1 that might be particularly important in an iodine deficiency setting. Polymorphisms in the DIO1 gene have been associated with changes in serum thyroid hormone levels, whereas decreased D1 activity has been reported in the nonthyroid illness syndrome and in several human neoplasias. The current review aims at presenting an updated picture of the recent advances made in the biochemical and molecular properties of D1 as well as its role in human physiology.

Introduction

Thyroid hormones are critical to the development and metabolism of virtually all tissues. Although the human thyroid gland mainly secretes thyroxine (T4), thyroid hormone actions are mediated by the active hormone, triiodothyronine (T3). In euthyroid individuals, the conversion of peripheral T4 to T3 accounts for 80% of all the T3 produced. This critical step in thyroid hormone metabolism is catalyzed by two enzymes, the type 1 and type 2 iodothyronine deiodinases (D1 and D2), via outer (5) ring deiodination of the pro-hormone T4. Type 3 iodothyronine deiodinase (D3) catalyzes the inner (5) ring deiodination of T4 and T3, thus inactivating the thyroid hormone action. In the last decades, several studies have extended our understanding on the mechanisms of D1 function in humans, underlying its effects on normal hormone metabolism and pathological processes. D1 is the only selenodeiodinase that can function as either an outer- (5) or an inner (5) ring iodothyronine deiodinase and was the first to be cloned (Berry et al. 1991a, Mandel et al. 1992). D1 is believed to provide a significant portion of the circulating plasma T3 in euthyroid vertebrates, including humans. Nevertheless, the remarkable preference of D1 for reverse T3 (rT3) as the enzymatic outer-ring deiodination substrate, as well as the deiodination of sulfated iodothyronines, argues for its role as a scavenger enzyme to deiodinate inactive iodothyronines, thus clearing these compounds from the circulation and serving, if necessary, to recycle iodine within the organism (Schneider et al. 2006). More recently, attention has been turned to the role of D1 in the biosynthesis of thyronamines, a newly identified class of endogenous compounds that appears to antagonize thyroid hormone actions (Scanlan et al. 2004).

The genetic background influences serum thyroid hormone profile. Single nucleotide polymorphisms (SNPs) in the deiodinase genes may interfere in the phenotypic expression of these enzymes influencing the levels of thyroid hormone. Indeed, several SNPs have been identified in the DIO1 gene and associated with changes in circulating thyroid hormone...
levels. Of note, it is remarkable that no inherited deficiency or mutation in human deiodinase genes has been reported so far. Pathologically increased thyroidal D1 activity plays a key role in the elevated serum T3 concentrations observed in hyperthyroid patients. Conversely, impaired D1 activity is likely to contribute to the lower levels of serum T3 in the nonthyroid illness syndrome. Because thyroid hormone influences the vital balance between cell proliferation and differentiation, deiodinases might also play a role in controlling the intracellular levels of thyroid hormone levels in tumorigenesis. Decreased D1O1 expression has been suggested as a marker of the epithelial follicular thyroid cell dedifferentiation, and even though the reasons for that remain speculative, it is striking that lower D1 expression has been described in almost all tumors derived from parenchymal or epithelial tissues.

This review aims at presenting an updated picture of the recent advances of our knowledge regarding the role of deiodinase type 1 as a regulator of thyroid hormone metabolism in human physiology and disease.

**Genetic, biochemical, and molecular properties of type 1 deiodinase**

The human DIO1 gene is located in the p32–p33 region on chromosome 1 and consists of four exons (Jakobs et al. 1997a). The mRNA size is about 2–2 kb with a UGA selenocysteine (Sec) codon in the region encoding the active center (Berry et al. 1991b). The TGA codon for the incorporation of Sec is located on the second exon (Mandel et al. 1992, Jakobs et al. 1997b). The encoded 27 kDa D1 protein is highly similar in size (26–30 kDa) and sequence among species with a few informative exceptions (Berry et al. 1991a, b, Mandel et al. 1992, Maia et al. 1995a, Sanders et al. 1997). The D1 protein contains a critical Sec residue at position 126 and is exceptionally sensitive to inhibition by propylthiouracil (6-n-propyl-2-thiouracil, PTU; Mandel et al. 1992). The human DIO1 gene is under the control of GC-rich SP1 promoters and contains two thyroid hormone response elements (TREs), both contributing to the T3 responsiveness of the human DIO1 promoter (Toyoda et al. 1995, Zhang et al. 1998).

In vertebrates, D1 is mainly expressed in liver and kidney, whereas in adult mammals, the Dio1 transcripts are also identified in thyroid, pituitary gland, intestine, placenta, and gonads (St Germain & Galton 1997, Bates et al. 1999, Wagner et al. 2008). An interesting study that evaluated the expression profile of all three deiodinases in a wide spectrum of rat tissues showed that D1 is the only deiodinase expressed in liver, kidney, and intestine at all stages of development (Bates et al. 1999). Both D1 mRNA and activity are present at low levels during fetal development and increase at later life stages, suggesting that D1 expression is regulated at least in part at a pretranslational level. The only exception for this expression pattern seems to be the testis, which presents higher levels of D1 activity in neonatal and weanling life (Bates et al. 1999, Wagner et al. 2008). Data on the ontogeny of the deiodinases in human fetal tissues are limited. On the basis of high levels of rT3 and T3 sulfate (T3S) observed in the human fetus, low levels of D1 activity are predicted, which progressively increase during the late gestational period and after birth (Santini et al. 1999). Indeed, hepatic D1 expression has been detected in the second gestational trimester at similar levels as observed in newborns, being around 20% of that found in adult liver (Huang et al. 1988, Richard et al. 1998). Of note, D1 is undetectable in human fetal brain tissues (Kester et al. 2004).

D1 is a thioredoxin (Trx)-fold integral membrane protein with a single transmembrane segment presented in the N-terminus and several clusters, corresponding to core secondary structures that compose the deiodinase globular domains (Callebaut et al. 2003). Studies using confocal microscopy of transiently expressed D1 in the human embryonic kidney cell line (HEK-293) indicate that it is localized in the plasma membrane with a cytosolic catalytic site (Baqui et al. 2000). The half-life of D1 protein is >12 h and its inactivation and subsequent degradation is enhanced by substrates such as iopanoic acid or rT3 but is apparently not...
susceptible to ubiquitination (St Germain 1988, St Germain & Croteau 1989, Gereben et al. 2000). It is still unclear whether the inactivated D1 can be reactivated in vivo, but continued protein synthesis is probably required for the maintenance of D1 activity. As shown in Fig. 1, D1-catalyzed reaction follows ping-pong kinetics with two substrates: the first being the iodothyronine and the second being an as yet unidentified endogenous intracellular thiol cofactor (Visser et al. 1976, 1978, Chopra et al. 1978, Leonard & Rosenberg 1980, Berry et al. 1991c). The catalytic cycle of D1 comprises two half-reactions: first, there is transference of I\(^+\) from the substrate to selenolate (Se\(^-\)), resulting in an intermediate compound that is immediately reduced by the cofactor generating a selenium iodide (SeI) complex. The proposed mechanism of the enzymatic reaction for the D1 enzyme involves the interaction of the sulphydryl group of the enzyme cysteine (Cys) residue with the second substrate. In this case, the as yet undefined cofactor would act as a reducing agent releasing iodine from the Sec residue and regenerating the active enzyme (Goswami & Rosenberg 1984, Berry et al. 1991c, Sun et al. 1997). Early studies on the D1-catalyzed reaction suggested that the endogenous cofactor might be glutathione (GSH) or Trx because both were effective in supporting catalysis (Goswami & Rosenberg 1987).

The reaction follows ping-pong kinetics with two substrates: the first being the iodothyronine and the second being an as yet unidentified endogenous intracellular thiol cofactor (Visser et al. 1983, Visser et al. 1988, Toyoda et al. 1997). Inner-ring deiodination of T3S by human and rat D1 is nearly 40 times faster than that from T3 (Otten et al. 1984). The same is observed for T4S and T2S. Of interest, T4 can serve as a substrate for the induced low Km processes, but, in this case, Km values were dependent on the artificial cofactor (dithiothreitol, DTT) concentrations (Sharifi & St Germain 1992). Conjugation of the phenolic hydroxyl with sulfate markedly enhances the suitability of the iodothyronine substrates for D1-catalyzed 5’ deiodination (Otten et al. 1983, Mol & Visser 1985). This is reflected in a markedly higher V\(_{\text{max}}\)/Km ratio for those substrates. Sulfation of T3 also clearly enhances the inner-ring deiodination, but the preference of D1 for T3S is much lower than that for rT3 or rT4S. The rate-limiting steps in the sulfation or desulfation of iodothyronines in a given tissue should be kept in mind when trying to predict the effects of D1-catalyzed deiodination.

Table 1 summarizes molecular and biochemical characteristics of the human D1.

Table 1  Molecular and biochemical properties of the human type 1 deiodinase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Property</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Reaction catalyzed</td>
<td>5- or 5’-deiodination</td>
<td>Jakobs et al. (1997a)</td>
</tr>
<tr>
<td>Chromosomal location</td>
<td>1p32-p33</td>
<td>Mandel et al. (1992)</td>
</tr>
<tr>
<td>Molecular mass</td>
<td>28-3 kDa</td>
<td>Baqui et al. (2000)</td>
</tr>
<tr>
<td>Subcellular location</td>
<td>Plasma membrane with the catalytic center in the inner surface</td>
<td>Otten et al. (1983, 1984) and Toyoda et al. (1997)</td>
</tr>
<tr>
<td>Substrate preference</td>
<td>rT(_3) &gt; T(_3)S &gt; T(_4) (5’)</td>
<td>Visser et al. (1988)</td>
</tr>
<tr>
<td>K(_m)(^a)</td>
<td>rT(_1) (5’): 0-21 (\mu)M</td>
<td>Visser et al. (1988)</td>
</tr>
<tr>
<td>Cofactor</td>
<td>Endogenous: unknown</td>
<td>Mandel et al. (1992) and Santini et al. (1999)</td>
</tr>
<tr>
<td>Tissue distribution Inhibitors</td>
<td>Artificial: dithiothreitol (DTT)</td>
<td>Berry et al. (1991c) and Mandel et al. (1992)</td>
</tr>
<tr>
<td>PTU</td>
<td>Liver, kidney, thyroid, and pituitary</td>
<td>Toyoda et al. (1995), Jakobs et al. (1997b) and Zhang et al. (1998)</td>
</tr>
<tr>
<td>Gold and iopanoic acid Regulatory factors</td>
<td>Uncompetitive inhibition</td>
<td>Ishii et al. (1983) and Beech et al. (1995)</td>
</tr>
<tr>
<td>Upregulation</td>
<td>Competitive inhibition</td>
<td>Schreck et al. (1994) and Toyoda et al. (1995)</td>
</tr>
<tr>
<td>Down regulation</td>
<td>Selenium deficiency</td>
<td>Beech et al. (1995)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jorgersen et al. (1989) and Alcantara et al. (2006)</td>
</tr>
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<td></td>
<td></td>
<td>Corvilain et al. (1993) and Duntas (2010)</td>
</tr>
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\(^a\)5 \(\mu\)M DTT.
Regulation of type 1 iodothyronine deiodinase expression

The expression and activity of D1 are modulated by a variety of hormonal, nutritional, and developmental factors, the most potent being thyroid hormone (Harris et al. 1978, Kaplan & Utiger 1978, Maia et al. 1995b, Koening 2005). The T₃ effect in rat and mouse Dio1 gene is due to transcriptional activation and does not require protein synthesis (Berry et al. 1990, Maia et al. 1995c). T₃ also positively regulates the human DIO1 gene at the transcriptional levels by interaction with two complex TREs located in the promoter region (Toyoda et al. 1995, Jakobs et al. 1997b, Zhang et al. 1998). In addition, the human DIO1 promoter contains thyroid hormone response-retinoic acid (RA) response elements that mediate thyroid hormone receptor (TR)β activation (Schreck et al. 1994, Toyoda et al. 1995). Interestingly, a recent report indicates that, in mice, the promoter of the Dio1 gene is also regulated by the hepatocyte nuclear factor 4α (HNF4α; Ohguchi et al. 2008). Based on the findings of that study, HNF4α would play a role in thyroid hormone homeostasis by cooperatively regulating the 5'-deiodination of T₄ with GATA4 and T₃-inducible Krüppel-like transcription factor 9 (KLF9). The authors also suggest that the T₃ regulation of Dio1 gene is probably due to an indirect mechanism that involves the T₃-dependent stimulation of KLF9 expression (Ohguchi et al. 2008).

In addition to thyroid hormones, other physiological compounds modulate D1 expression (Table 1). The administration of GH to euthyroid adults is known to increase the ratio of plasma T₃ to T₄ whereas reducing that of rT₃ to T₄ (Jorgensen et al. 1989, Alcantara et al. 2006), in a peripheral mechanism that probably involves augmented D1 and/or a reduction in D3 activity (Darras et al. 1992, Van der Geyten et al. 1999). TSH also induces D1 synthesis in the human thyroid gland, by a mechanism that involves, at least in part, the second messenger cAMP, via a protein synthesis-dependent process (Ishii et al. 1983, Pekary et al. 1994, Beech et al. 1995). Although the mechanism for the stimulation of Dio1 transcription by cAMP has not been fully elucidated, its effects are additive to that of T₃, resulting in a fivefold stimulation relative to control (Mori et al. 1996).

Data on the effects of glucocorticoids on D1 expression are controversial. Although some in vitro studies have shown that glucocorticoids induce Dio1 mRNA and activity in rat liver, others described no changes in D1 activity (Menjo et al. 1993, Van der Geyten et al. 2005). Studies using rat liver and kidney cell cultures observed an increase of Dio1 mRNA and activity after incubation with dexamethasone (Davies et al. 1996b). Controversially, studies on a pituitary rat cell line found that dexamethasone alone had no effect on Dio1 gene expression but did enhance the effect of T₃ (Maia et al. 1995b). On the other hand, the administration of dexamethasone to euthyroid adult males increased the circulating rT₃ and rT₃/T₄ ratios, which could be a result of the augmented production of rT₃ instead of decreased clearance (LoPresti et al. 1989).

Deiodinases are selenoproteins and, thus, susceptible to selenium deficiency. The effect of selenium deficiency on the synthesis of intracellular selenoproteins is apparently tissue dependent, being more pronounced in liver, skeletal muscle, and heart (Meinholds et al. 1992, Bermano et al. 1995, Bates et al. 2000). In rats, selenium deficiency decreases D1 activity in liver and kidney by a mechanism that involves protein translation, secondary to a blockage in the Sec incorporation (Beckett et al. 1987, DePalo et al. 1994). The administration of T₃ did not affect D1 activity in the selenium-deficient rats, whereas selenium-fed controls had a twofold increase in enzymatic activity. Mice with excessive iodine intake presented a decreased selenium concentration in urine and liver and reduced renal and hepatic D1 mRNA and activity levels (Yang et al. 2006). The selenium supplementation corrected these alterations. In humans, selenium deficiency is observed in subjects receiving diets with restricted protein content, such as those given for phenylketonuria, and also in elderly patients (Kauf et al. 1994, Calomme et al. 1995, Lombeck et al. 1996, Jochum et al. 1997). Seleno-deficient individuals have mildly elevated serum T₄ and T₄ to T₃ ratios, but normal TSH. Indeed, the deficiency of this essential micronutrient has been implicated in the pathogenesis of myxedematous endemic cretinism, prevalent in African endemic goiters, and associated to a thyroid ‘exhaustion’ atrophy occurring near birth. This might result from the low resistance of a fragile tissue to enhanced H₂O₂ generation under intense thyroid stimulation by high TSH levels (Goyens et al. 1987, Vanderpas et al. 1990, Duntas 2010). Of note, deterioration of thyroid function was observed after selenium administration to iodine-deficient people in an African region of endemic goiter, suggesting that the reduction in D1 activity during selenium deficiency can protect against iodine deficiency, presumably by reducing the deiodination of T₄, T₃, or T₃S (Contempre et al. 1991, 1992).

Role of D1 deiodinase in thyroid hormone activation and inactivation

The functional role of D1 in humans remains a matter of debate. Nearly 80% of peripheral T₃ originates from deiodination of the pro-hormone T₄ by D1 and D2. However, the relative roles of D1 versus D2 in extrathyroidal T₃ production are still controversial. Probably because D1 was the first selenodeiodinase to be identified and because of its subcellular location, it was often assumed that the majority of circulating T₃ was derived from T₄ via D1 activity. Nevertheless, the long-life of D1 protein and T₃ upregulation of D1 activity, just the opposite of what would be expected in a typical feedback loop, raise some questions about this assumption. Moreover, clinical studies have showed a maximum decrease of 25% in serum T₃ in athyreotic, T₄-replaced, euthyroid individuals treated with higher doses of PTU (Geffner et al. 1975, Saberi et al. 1975). Indeed, subsequent cumulative data on the biochemical and molecular properties of D2 indicate that this enzyme also contributes a significant portion of serum T₃ levels in humans.
The D1 enzyme seems extremely inefficient in carrying out this reaction when compared with the D2, which has a 700-fold greater catalytic efficiency for $5'$-deiodination of T₄ (Maia et al. 2005). First, in contrast with D2-catalyzed reaction that generates 1 mol of T₃ for each T₄ molecule, for each 2 moles of T₄ deiodinated by D1, only 1 mol of T₃ and a second of rT₃ is produced since D1 catalyzes the inner- and outer-ring deiodination of T₄ equally well, as predicted from $V_{max}/K_{m}$ estimates (Visser et al. 1988). This can explain a catalytic efficiency difference of 2, whereas the rest is primarily due to the much slower rate of D1-catalyzed T₄ to T₃ conversion under physiological conditions. This is not easily observed under typical in vitro assay conditions because the catalytic activity of this enzyme significantly varies from the artificial DTT generally used to other cofactor candidates such as GSH, as well as with variations of the cofactor concentrations (Goswami & Rosenberg 1987, Goemann et al. 2010).

The human D1–or D2-derived T₃ production significantly varies according to the thyroid status. Because DIO1 expression is positively regulated by thyroid hormone, D1-catalyzed T₄ to T₃ reaction is expected to be decreased in the hypothyroid state (Maia et al. 1995c, Kim et al. 1998). In contrast, increased D2-catalyzed T₄ to T₃ conversion is anticipated due to the increase in the half-life of D2 protein and DIO2 transcription secondary to the decreased levels of free T₄ (FT₄) and T₃ (FT₃) respectively (Gereben et al. 2000, Bianco et al. 2005, Wagner et al. 2007). In the opposite direction, D1-catalyzed T₃ production would predominate in the hyperthyroid state (see below). These assumptions are consistent with the predicted increased efficiency of D2-catalyzed T₄ to T₃ conversion as demonstrated in early studies; these studies showed that in hypothyroid patients, the fractional whole-body conversion rate of T₄ to T₃ was 42%, whereas this rate fell to 21% in the same patients made euthyroid by L-T₄ replacement therapy (Inada et al. 1975). Sustained elevations in serum T₃/T₄ ratios have also been reported in athyreotic subjects partially withdrawn from T₄ therapy (Lumi et al. 1984).

In addition to the importance of the D1 and D2 in converting T₄ to T₃ in peripheral tissues, these enzymes are also highly expressed in the thyroid gland (Leonard & Visser 1986, Toyoda et al. 1992, Schoenmakers et al. 1995, Salvatore et al. 1996, Leonard et al. 2001). D1 seems to be constitutively expressed in the human thyroid gland, whereas D2 expression varies closely with the degree of thyroid stimulation (Salvatore et al. 1996). The thyroidal contribution for overall thyroid hormone economy is estimated on two-thirds from hydrolysis of thyroglobulin and one-third from deiodination (Laurberg et al. 2007). Interestingly, perfusion studies demonstrated that dog and human thyroid have a preferential secretion of T₃, favoring a more pronounced D1 activity in this gland (Laurberg 1978, Tegler et al. 1982).

The distinct subcellular localization of D1 and D2 might also contribute to its functional roles. D1 is located in the inner surface of the plasma membrane, whereas D2 is in the endoplasmic reticulum (Baqui et al. 2000), which could explain the early observations that T₃ generated by D1 rapidly equilibrates with plasma T₃. Moreover, this deiodinase seems to be positioned much better to clear rT₃ and other compounds from the circulation (Toyoda et al. 1997). The role of the facilitated deiodination of sulfated iodothyronines might be the recovery of the trace element iodine from inactive hormone metabolites, reutilized for T₄ synthesis (Toyoda et al. 1997). On the other hand, D2-derived T₃ production has a greater effect on T₃-dependent gene transcription than that from D1, which indicates that generation of nuclear T₃ is an intrinsic property of the D2 protein (Maia et al. 2005).

Important insights into the role of D1 for thyroid hormone metabolism were also obtained from two genetically modified animal models: C3H strains, which present inherited low D1 expression in liver and kidney, and D1KO mice, with targeted disruption of the Dio1 gene (Berry et al. 1993, Schoenmakers et al. 1993, Schneider et al. 2006). The reduced D1 activity in C3H mice correlates with a CGT repeat insertion into the 5'-flanking region of the Dio1 gene that seems to impair C3H promoter potency (Maia et al. 1995a). Both the strains have elevated serum total and FT₄ and rT₃ but normal serum-FT₃ and TSH concentrations. The normal FT₃ concentration in these mice could be explained by the fact that, although the fractional conversion of T₄ to T₃ per day would be reduced, the higher FT₄ concentration permits normal daily T₃ production. In addition, serum T₃ levels were significantly higher in C3H than in C57 mice after the same dose of exogenous T₃, suggesting a reduction in T₃ clearance that might contribute to the maintenance of serum T₃ concentrations (Maia et al. 1995a). However, the rate of disappearance of T₃ was comparable in euthyroid WT and D1KO mice (Schneider et al. 2006). A potential source of serum T₃ in both C3H and D1KO mice is D2-catalyzed T₄ to T₃ conversion. Indeed, it has been shown that, despite the higher serum-FT₄, the levels of D2 activity in brown adipose tissue of C3H mice are comparable to those observed in C57 animals (Wagner et al. 2007). The normal serum-FT₃ levels would lead to a euthyroid state in peripheral tissues and can account for the observed euthyroid phenotypes in both phenotypes. Of note, no cases of inherited D1 deficiency in human have been documented so far.

In the last decade, animal models with deficiency of both D1 and D2 enzymes were generated (Christoffolete et al. 2007, Galton et al. 2009). The C3H–D2KO mouse (targeted disruption of the Dio2 gene and genetically low D1 expression) has hepatic and renal D1 activities lower than those observed in wild-type mice (C57/BL6) but unexpectedly higher than those of the C3H mice. These mice present euthyroid serum T₃ levels and serum T₄ levels even more augmented than in the C3H. The serum TSH is increased, which could be important to maintain euthyroid serum T₃ concentrations. The double D1/D2KO mice are also able to maintain a normal serum T₃ level and their general health, growth, and reproductive capacity are seemingly
unimpaired (Galton et al. 2009). The authors underline the feature that D1 and D2 enzymes might not be essential to the maintenance of normal plasmatic T3 levels in the rodent as long as the hypothalamic–pituitary–thyroid axis is intact. These alterations, however, might not perfectly reflect those putatively found in humans, because the rat thyroid is responsible for 50% of the circulating T3, whereas humans depend more on peripheral deiodination, given that only 20% of the T3 is derived from the thyroid gland.

Iodine is essential for thyroid hormone synthesis, and iodine deficiency leads a series of physiological adaptations in the hypothalamic–pituitary–thyroid axis in an attempt to maintain plasma and tissue T3 in the normal range. The earliest thyroid modification is a decrease in 3,5-diiodothyronine, with a consequent decrease in the thyroidal T4, whereas thyroidal T3 remains constant (Riesco et al. 1976). Indeed, elevated plasma TSH, associated with decreased serum T4 and a virtually unchanged T3, are the physiological hallmarks of moderate iodine deficiency as well as of the early phases of primary hypothyroidism. In both situations, however, the extrathyroidal changes are complex and involve a high degree of tissue specificity. It is observed that although D1 and D3 activity is unchanged in marginal iodine deficiency, D2 activity is markedly upregulated in D2-expressing tissues, thus increasing the proportion of T3 formed locally and mitigating the decreases in tissue T3 content (Larsen et al. 1981, Jansen et al. 1994, Schröder-van der Elst et al. 1998). Interestingly, however, increase in liver D1 activity has been observed in severe iodine-deficient rats under selenium supplementation (Arthur et al. 1991). Of note, studies in the D1KO mouse demonstrated that iodothyronines other than T4 are the substrates for 5′-deiodination by D1 enzyme, which releases iodine back into the circulation (Schneider et al. 2006). In the absence of D1, inactive and lesser iodothyronines escape deiodination and are excreted in the feces with the potential loss of the associated iodine. This scavenging function of D1 might be particularly important in the iodine deficiency setting (Galton et al. 2009).

Recently, attention has been turned to a potential role of D1 in the biosynthesis of thyronamines (3-iodothyronamine, 3-T1AM, and thyronamine, T0AM), a newly identified class of endogenous compounds that seem to be isozyme-specific substrates of deiodinases (Scanlan et al. 2004, Piehl et al. 2008, Scanlan 2009). These molecules are chemical derivatives of thyronines, the principal chemical form of T4 that appears to antagonize the typical actions of thyroid hormones. It has been shown that the iodothyronamines have Vmax/Km values comparable to the corresponding iodothyronide, indicating that they would be as readily deiodinated as iodothyronides by the appropriate deiodinase isoenzyme (Piehl et al. 2008). Nevertheless, unlike T4, T3AM is not a substrate for D1 or D2 enzymes. Instead, T3AM is readily deiodinated to 3,3′,5′-triiodothyramide (rT3AM) by D3, and rT3AM can be further deiodinated to ultimately provide T1AM. Using HepG2 cell lysates or mouse liver membrane fractions, D1 was able to use rT3AM or 3,3′,5′-triiodothyramine (3′,5′-T2AM) as substrates and both reactions were sensitive to PTU. On the other hand, T1AM is the most efficiently processed thyronamine substrate using a sulfotransferase preparation from human liver, and the Vmax/Km value for T1AM compares to that of T3, suggesting that similar to T3, sulfation of T1AM may be an important clearance mechanism for regulating free circulating levels (Piehl et al. 2008). The physiological role of thyronamines is uncertain, but pharmacological data show that a single-dose T1AM administration in vivo induces intense hypothermia and bradycardia, leading to a hypometabolic state that may confer a potential neuroprotective benefit in cases of ischemic injury (Scanlan et al. 2004).

Indeed, T3AM treatment was found to reduce infarct volume by 40% in a middle cerebral artery occlusion stroke model in mice. Interestingly, the degree of neuroprotection afforded by T1AM was correlated with the magnitude of T1AM-induced hypothermia (Doyle et al. 2007). These findings indicate the existence of an exciting signaling pathway that leads to rapid physiological effects that are opposite to those produced by thyroid hormone excess (Scanlan 2009). Nevertheless, as pointed out by the authors, the precise relationship between T1AM and thyroid hormone remains poorly understood, and there is currently no direct evidence for in vivo thyroid hormone-derived synthesis of thyronamines.

Role of type 1 deiodinase in human disease

DIO1 polymorphisms

As stated above, no cases of inherited D1 deficiency have been reported so far and, remarkably, no mutations have been identified in any of the deiodinase enzyme-encoding genes to date. In contrast, however, several genetic variations have been described in DIO1 and DIO2 genes, which may influence circulating or intracellular thyroid hormone levels (Peeters et al. 2006, Butler et al. 2010, Dora et al. 2010).

Two SNPs in the human DIO1 gene, D1a-C/T (variation at the nucleotide position 785 of the D1 eDNA sequence – C785T) and D1b-A/G (variation at the position 1814 – A1814G), have been associated with changes in serum rT3 levels (Peeters et al. 2003a). Each T-allele of D1a-T (frequency of 34%) was associated with an increase of ~2 ng/dl in plasma rT3 levels, whereas the less frequent G allele of D1b (10.3%) was associated with lower rT3/T4 and higher T3/rT3 plasma ratios. In the elderly, carriers of the D1a-T allele had higher serum-FT4 and rT3, lower T3, and lower T3/rT3, whereas the D1b-G allele was associated with higher serum T3 and T3/rT3 (de Jong et al. 2007). Consistently with a lower D1 activity for the DIO1–785T, a recent study has shown that the administration of T3 to individuals harboring this variant was associated with enhanced potentiation of the effect of the antidepressant sertraline (Cooper-Kazaz et al. 2009). The genetic influence of these polymorphisms in healthy Danish twins has also been addressed and revealed that carriers of the DIO1–785T allele had 3-8% higher FT4 and 14-3% higher rT3.
levels, resulting in a lower $T_3/T_4$ and $T_3/rT_3$ ratio and a higher $rT_3/T_4$ ratio. The $D1b$-$A/G$ polymorphism, however, was not associated with changes in serum thyroid hormone levels (van der Deure et al. 2009). As both SNPs are located in the 3'UTR, it has been speculated whether the mRNA stability would be compromised or affect mRNA folding, which is necessary for the incorporation of Sec in the catalytic center of the protein (Peeters et al. 2003a).

The $D1a$-$C/T$ and $D1b$-$A/G$ polymorphisms have also been associated with changes in free insulin-like growth factor 1 (IGF1) levels (Peeters et al. 2005a). Based on the data derived from the four haplotype alleles and corresponding serum thyroid hormone levels in two different populations, the authors assumed that the haplotype $D1a$-$T/D1b$-$A$ is associated with decreased $D1$ activity, whereas patients with the haplotype $D1a$-$C/D1b$-$G$ displays increased $D1$ levels. The $D1a$-$T/D1b$-$A$ haplotype was associated with higher levels of free IGF1 levels, which could serve as a tentative mechanism for normalization of $D1$ activity. Of note, this haplotype showed an allele dose effect on serum $T_3$ concentrations in elderly men (resulting in lower levels of $T_3$) but not in the population constituted by healthy blood donors.

Recently, a new polymorphism $A/C$ located in intron 3 of the human $DIO1$ gene has been described (Panicker et al. 2008). This polymorphism was associated with increased FT$_3$ and decreased FT$_4$ and $rT_3$ levels not only in patients receiving thyroid hormone replacement therapy but also in a large group of healthy individuals. Of interest, in both the groups, the former described that $D1a$-$C/T$ SNP also leads to variations in $T_3$, FT$_4$, and $rT_3$ levels, although in a less pronounced fashion (Peeters et al. 2003a, de Jong et al. 2007, Panicker et al. 2008). The effect of the $A/C$ polymorphism is consistent with the $C$-allele being associated with higher $D1$ enzymatic activity. Although the mechanism by which this polymorphism affects deiodinase function remains unknown, the authors estimate that it accounts for nearly 2% of genetic variance of FT$_4$ and 1.5% of FT$_3$.

**Graves’s hyperthyroidism and multinodular goiter**

It is well established that hyperthyroid patients suffering from Graves’ disease or multinodular toxic goiter have a disproportionate increase of serum $T_3$ as compared with the increase in serum $T_4$ (Larsen 1972, Nicoloff et al. 1972, Woebber 2006). In both diseases, thyroid hormone production is no longer targeted to physiological needs; instead, it is driven by a number of abnormalities. In Graves’ disease, the abnormal generation of stimulating antibodies of TSH receptor is implicated (Davies et al. 2005, Laurberg et al. 2008), whereas in multinodular goiter, a constitutive activation of the thyroid follicular cells occurs (Krohn et al. 2005).

Thyroid hormone excess could be a result of either increased thyroidal $T_3$ production or elevated quantities of $T_3$ from peripheral $T_4$ to $T_3$ conversion. This central question was recently addressed by Laurberg et al. (2007) in untreated patients with Graves’ disease or multinodular goiter. In agreement with earlier studies (Abuid & Larsen 1974), it was observed that patients treated only with PTU, a specific inhibitor of $D1$, presented a rapid and sustained fall in serum $T_3$ levels of ~57%, whereas those treated with a combination of PTU plus potassium iodine or sodium ipodate, which inhibits both D1 and D2 and several processes involved in thyroid hormone production and secretion respectively, present an additional fall of ~20%.

Considering that the secretion of intrathyroidal and peripheral $T_3$ is selectively inhibited by PTU, the authors demonstrated that $D1$ deiodination has a crucial role in $T_3$ generation in these diseases. In fact, although thyroidal $D1$ contributes 6% of daily thyroidal normal $T_3$ production, this can increase to around 57% in patients with severe hyperthyroidism, suggesting that the major source of serum $T_3$ in hyperthyroid patients is the thyroid gland as a consequence of increased thyroidal $D1$ (Fig. 2). The remainder of the thyroidal $T_3$ production is derived from thyroglobulin, with a nearly doubled $T_3$ to $T_4$ ratio, plus fractional $T_4$ to $T_3$ conversion in the peripheral tissues. As

![Figure 2](https://example.com/figure2.png)  
**Figure 2** Schematic representation of the estimated sources of $T_3$ production in euthyroid and hyperthyroid state. The thyroidal contribution to serum $T_3$ levels increases in parallel with the disease severity, reaching nearly two-thirds of the total $T_3$ production in severe hyperthyroidism (derived from Laurberg et al. 2007).
liver and kidney D1 increases in the presence of excessive thyroid hormone levels, this enzyme is also responsible for the majority of the peripheral T₃ production (Maia et al. 2005, Laurberg et al. 2007). These observations support the choice of PTU as the preferred thionamide for therapy in severe hyperthyroidism or thyroid storm (Maia 2007). Nevertheless, methimazole is superior to PTU during chronic therapy (Nakamura et al. 2007). The reasons are the longer duration of methimazole action that favors better compliance and improves prognosis and the lower frequency of side effects compared with PTU. Moreover, the relatively low doses of PTU used in chronic therapy will not effectively inhibit D1.

The high thyroidal T₃ production might explain the pattern of persistently high serum T₃ with normal or low serum T₄ levels during treatment observed in a minority of patients with T₃-predominant Graves’ disease. Recently, D1 and D2 activities were evaluated in samples of thyroid tissue from patients with T₃-predominant Graves’ disease pretreated with methimazole before thyroidectomy (Ito et al. 2011). Intriguingly, not only an augmented activity of both enzymes but also a correlation between the thyroidal D2 activity and serum FT₃ to FT₄ ratio was observed, even more robust than that of thyroidal D1 activity.

**Fasting and nonthyroidal illness syndrome**

Fasting and severe illness induce profound changes in the thyroid hormone economy marked by decreases in serum T₃ and T₄ levels without a compensatory rise in the serum TSH level in both animal models and humans (Leonard et al. 1991, Nishikawa et al. 1998). Indeed, the decrease in the concentration of circulating T₃ relative to that of T₄ and an increase in rT₃ concentrations in fasting humans was one of the earliest indications that the peripheral metabolism of thyroid hormones could be modulated by physiological or physiopathological events (Portnay et al. 1974). Nevertheless, the complex physiopathological mechanisms responsible for these systemic changes remain poorly understood (Warner & Beckett 2010). Changes in deiodinases expression have been postulated to play important roles in the altered circulating levels of thyroid hormones in fasting and nonthyroidal illness syndrome (NTIS) (Debaveye et al. 2008, Kwakkel et al. 2009). Decrease in T₃ production could be explained by decreased levels of D1 and/or D2, whereas the elevation of rT₃ could be due to decreased activity of D1 and the increase in D3 activity, which determines increased hormone degradation (Peeters et al. 2003b, 2005b).

In rodents, fasting induces decrease in liver and pituitary D1 activities. However, it is not established whether this reduction is due to a direct effect of fasting on D1 activity or secondary to the decreased levels of serum thyroid hormones, which is also observed in this situation (St Germain & Galton 1985, O’Mara et al. 1993, Aceves et al. 2003). Interestingly, it has been demonstrated that leptin, an adipocyte-derived hormone that is diminished in food deprivation, modulates the 5’-deiodinases in different tissues depending on the energetic status (Cabanelas et al. 2006). Leptin was shown to exert direct peripheral effects on deiodinase activity, positively regulating liver, kidney, and pituitary D1 activity in fed animals (Cabanelas et al. 2006).

Results with leptin replacement in fasting, however, have produced contradictory results depending on the tissue analyzed. Some studies failed to demonstrate a decrease in hepatic D1 activity on food-restricted animals in rats treated with i.c.v. leptin injection (Ahima et al. 1996, Legradi et al. 1997, Cusin et al. 2000), whereas others showed that the decrease in thyroid D1 is not restored by leptin replacement. In the latter, the authors suggest that the diminished D1 activity could result from the increased levels of corticosterone observed in these animals (Araujo et al. 2009). Conversely, rats with high-fat-induced obesity presented increased D1 activity in the thyroid, liver, and kidney and higher rates of oxygen consumption and energy expenditure, without changes in the thyroid hormone circulating levels (Araujo et al. 2010). In starved humans, circulating T₃ concentrations decrease rapidly to about 50% of control and remain low for up to 3 weeks of fasting (Vignati et al. 1978, Kaptein et al. 1985, Rosenbaum et al. 2005). However, the sustained decrease in serum T₄ and T₃ could also be due to increased thyroid hormone inactivation by D3 enzyme, as recently reported in other pathological situations (Olivares et al. 2007, Simonides et al. 2008).

An entire set of data obtained from critically ill patients demonstrated that patients with more pronounced alterations in serum thyroid parameters have a significantly higher mortality rate and that rT₃ and T₃/rT₃ are prognostic factors for survival (Peeters et al. 2005a). Critically ill patients showed reduced hepatic D1 activity, which was negatively correlated with T₃ and rT₃ plasma levels. Interestingly, D1 activity in liver was lowest in patients who died of cardiovascular collapse and highest in patients who died of brain damage. Lower D1 activity was also observed in patients with acute renal failure and in those receiving inotropes, compared with those who did not require these treatments (Peeters et al. 2003b). In contrast, other studies found no differences in D1 activity measured in the subcutaneous adipose tissue in patients in intensive care units, suggesting that thyroid hormone bioavailability might be regulated in a tissue-specific way (Rodriguez-Perez et al. 2008).

Cytokines, such as IL1, IL6, TNFα, have been postulated as potential mediators of the alterations in thyroid function that occur during severe illness (Chopra et al. 1991, Boelen et al. 1993, Pekary et al. 1994). Studies in health volunteers demonstrated that a single dose of IL6 caused a transient decrease in serum T₃ and TSH (Torpy et al. 1998), changes that are characteristic of the NTIS. In hospitalized patients, there is also an inverse correlation between the serum IL6 and the T₃ concentrations (Boelen et al. 1993, 1995, Davies et al. 1996a). These proinflammatory molecules seem to inhibit the expression and function of D1 in human hepatocarcinoma.
cells (HepG2; Jakobs et al. 2002), whereas studies on rat hepatocytes have demonstrated that IL1 and IL6 impair the T3 induction of D1 mRNA by a mechanism that involves a functional disruption of steroid receptor coactivator 1 (SRC-1)–thyroid hormone receptor interaction caused by competition between IL1 and T3–stimulated transcriptional events for limiting quantities of SRC-1 (Yu & Koenig 2000, Jakobs et al. 2002). The T3 inhibitory effect of IL1β was salvaged by coexpression of the nuclear SRC-1 but not by cAMP response element binding protein (Yu & Koenig 2006).

The effects of TNFα have been examined in hepatocytes and HepG2 cells with contradictory results. TNFα decreased the T3–stimulated D1 mRNA in HepG2 cells (Nagaya et al. 2000). In a second study in dispersed rat hepatocytes, IL1β and IL6 blocked the T3 induction of D1 mRNA and activity but TNFα had no effect on D1 expression (Yu & Koenig 2000). The contradictory effects observed could be due to differences in the experimental paradigms. Despite this, both studies suggest that a mechanism for acute decrease in D1 expression during illness could be competition for limited amounts of one or more transcription factors that are rate limiting for both cytokine- and T3–dependent transcriptional events. In has been shown in in vitro studies that IL1β stimulates both D1 and D2 expression (Baur et al. 2000).

**Human neoplasias**

The balance between proliferation and differentiation is among the wide variety of biological events influenced by thyroid hormone and recent studies suggest that deiodinase enzymes might play an important role in the control of thyroid hormone metabolism and action during tumorigenesis. Studies focusing on DIO1 and DIO2 gene expression in benign and malignant thyroid tumors have demonstrated that D1 and D2 expression are diminished, whereas D3 is increased in tumoral tissue (Arnaldi et al. 2005, Meyer et al. 2007, Dentice et al. 2009).

Changes in D1 expression have been proposed as a marker of the epithelial follicular thyroid cell dedifferentiation (Schreck et al. 1994, Kohrle 1997, Meyer et al. 2007). Significant decreases in D1 mRNA and activity levels were demonstrated in samples of papillary thyroid carcinoma (PTC) as compared with adjacent normal thyroid tissues (de Souza Meyer et al. 2005). These results were observed in all histological subtypes, especially in the classical form of PTC, as well as in the different clinical stages (Ambrozik et al. 2005, Arnaldi et al. 2005, de Souza Meyer et al. 2005). In contrast to PTC samples, D1 levels were normal or increased in follicular thyroid adenoma, follicular thyroid carcinoma (FTC), and Hürthle cells carcinoma (Arnaldi et al. 2005, de Souza Meyer et al. 2005). These findings illustrate the distinct D1 expression patterns in PTC and follicular neoplasias, thus suggesting that downregulation of D1 expression is an early event in thyroid cell dedifferentiation toward PTC.

Although earlier studies reported that D1 activity was absent in samples of anaplastic thyroid carcinoma (ATC; Schreck et al. 1994), more recent studies reported high levels of D1 mRNA and activity in sample of a mixed anaplastic and Hürthle cell carcinoma (de Souza Meyer et al. 2005). Undifferentiated thyroid carcinomas are the end-stage forms of thyroid cancer and are believed to arise from papillary or follicular carcinomas. Based on the above observation, one could speculate that the lack of expression of this isoenzyme could be a marker of papillary origin.

Changes on D1 regulation were also documented in various thyroid cancer cells. Using cell lines of FTC (FTC–133 and FTC–238), Schreck et al. (1994) have demonstrated that D1 loses its responsiveness to TSH and T3 stimuli, but not to RA, a component that regulates growth rates and differentiation of several cell types. Low basal D1 activity, which is markedly increased by RA, was described in these cell lines but neither basal nor RA-inducible D1 activity is detected in cell lines derived from ATC (HTh 74 and C 643) (Schreck et al. 1994, Schmutzler et al. 2004). Proliferations of FTC–133 and FTC–238 cells were decreased by all-trans RA. Pretreatment of FTC–133 with RA resulted in a reduced tumor growth in xenotransplantation experiments as compared with untreated control cells (Schmutzler et al. 2004). These studies indicate that the coexpression of D1 and RA receptors in differentiated thyroid carcinoma preserves its basal regulatory functions in contrast to less differentiated thyroid neoplasias.

Downregulation of D1 expression was also reported in other human neoplasias. Lower levels of D1 mRNA were described in samples of renal clear cell carcinoma, the most frequent renal cancer (Pachucki et al. 2001). Interestingly, several variants of DIO1 transcripts were found in this type of neoplasias, all of them underexpressed in tumor tissue as compared with normal renal tissue. These findings suggest a possible role of disturbed expression of splicing factors splicing factor–2/alternative splicing factor (SF2/ASF) and heterogeneous ribonucleoprotein A1 (hnRNPA1) in samples of human renal cancer (Piekielko–Witkowska et al. 2009). Low levels of D1 expression were also demonstrated in liver carcinoma when compared with normal tissue (Sabatino et al. 2000). In addition, HepG2 cells exhibit high levels of D1 activity, which is stimulated by RA or T3 (Schreck et al. 1994, Toyoda et al. 1995). Hemangioma tissue presents nearly undetectable D1 activity compared with healthy liver tissue (Kornasiewicz et al. 2010). In addition, decreased D1 activity was described in pulmonary squamous cell cancer, adenocarcinoma (Wawrzynska et al. 2003), and prostate cancer (Dutkiewicz et al. 1995).

On other hand, mammary cancer induced in Sprague–Dawley mice with N-methyl-N-nitrourea had twice as much D1 activity when compared with normal, nonlactating tissue (Macejova et al. 2001). Interestingly, D1 levels were higher in 2- to 4-month-old tumors when compared with 6-month-old tumors (Macejova et al. 2001), characterizing a loss of D1 expression with tumor progression. Besides, the MCF–7 cells
(an ovarian hormone-dependent cell line derived from mammary cancer) also present D1 regulated by RA, although it does not respond to T3 or isoproterenol (Garcia-Solis & Aceves 2003). Similar to that observed in other cells lines, no detectable activity of D1 is present in less differentiated mammary cell lines (MDA-MB-231), either in basal conditions or under different treatments (Garcia-Solis & Aceves 2003). Human breast cancer tissue expresses high levels of D1 activity and mRNA, a profile unlike most other human tumors of epithelial origin (Debski et al. 2007).

D1 activity is found in normal pituitary as well as human pituitary adenomas. Although a wide variation on D1 activity among the tumor histological subtypes has been reported, the highest activities were seen in the thyrotroph and lactotroph adenomas. Approximately, half of these tumors presented D1 activities several-fold greater than any of the normal pituitary samples (Baur et al. 2002, Tannahill et al. 2002).

In summary, except for the follicular thyroid lesions and tumors originating in the mammary gland, D1 expression is decreased in the majority of human neoplasias of epithelial origin. Nevertheless, whether it is part or consequence of the neoplastic process still remains to be clarified. A possible explanation for the decreased D1 expression could be loss of physiological response to T3 due to aberrant expression of TRs or a high frequency of TR mutations, as reported in several human tumors (Cheng et al. 2010). One can also speculate that it is a result of the low intracellular T3 level secondary to D3 overexpression (Dentice et al. 2009). Nevertheless, because tumor tissue may represent a more homogeneous population of cells than normal tissue, we cannot rule out that changes in expression could also be secondary to a difference in the cell types, rather than a change in expression level in cancer cell itself.

Conclusion

Since the identification, several decades ago, of the type 1 deiodinase, a considerable amount of research has been carried out in an attempt to extend our knowledge of its molecular and biochemical properties as well as our understanding of its role in human thyroid hormone metabolism. This enzyme is a member of a family of oxidoreductases that contains the rare amino acid Sec in its active site and D1-catalyzed reaction follows ping-pong kinetics with two substrates: the first being the iodothyronine and the second being an endogenous intracellular thiol cofactor. Besides its capacity of outer-ring deiodination, which contributes to daily T3 production, D1 also catalyzes the iodine removal by inner-ring deiodination inactivating thyroid hormones. Indeed, the remarkable D1 preference for rT3 as the enzymatic outer-ring deiodination substrate as well as the deiodination of sulfated iodothyronines argues for a major scavenging function of this enzyme, namely the recovery of the trace element iodine from inactive hormone metabolites to be reutilized for thyroid hormone synthesis. This functional role can be particularly relevant in a setting of iodine deficiency.

A multiplicity of hormonal, nutritional, and developmental factors modulates D1 expression. Thyroid hormone is the most important physiological upregulator of D1 expression, and hypothyroidism is associated with low levels of D1 mRNA and activity. D1 activity is also susceptible to selenium deficiency, and selenium-deficient individuals have mildly elevated serum T4 and T4 to T3 ratios, but normal TSH.

Besides its role in human physiological control of peripheral thyroid hormone metabolism, alterations in D1 expression and activity have also been described in human diseases. Polymorphisms in DIO1 gene have been associated with changes on thyroid hormone levels, whereas augmented thyroidal D1-catalyzed T3 generation seems to play a major role in T3 overproduction observed in Graves’ disease and multinodular goiter. Decreased D1 expression has been implicated in the thyroid hormone changes observed in fasting and NTIS, whereas disturbed expression and regulation of this enzyme is reported in human neoplasias.

Nonetheless, there are still significant gaps in our knowledge of D1 function in human physiology. The endogenous cofactor is as yet unidentified, which may jeopardize conclusions obtained from in vitro studies using artificial conditions. The relative role of peripheral D1-catalyzed T3 production in human euthyroid state or in pathological processes, such as NTIS, is still a matter of debate. D1 expression is decreased in the majority of human tumors of epithelial origin but whether this occurs as an attempt to counter-regulate the proliferate state or contribute to the dedifferentiation process to the neoplasm remains to be determined. Further studies in the exciting field of thyroid hormone metabolism are warranted to unravel these unanswered questions.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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