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Mini-Review

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Deiodinases and Cancer

Annarita Nappi,[1] Maria Angela De Stefano,[1] Monica Dentice,[1] and Domenico Salvatore[2]

[1]Department of Clinical Medicine and Surgery, University of Naples "Federico II," Naples, Italy; and [2]Department of Public Health, University of Naples "Federico II," Naples, Italy.

ORCiD number: 0000-0002-4556-7620 (D. Salvatore).

Abbreviations: BCC, basal cell carcinoma; EMT, epithelial to mesenchymal transition; SCC, squamous cell carcinoma; Shh, sonic hedgehog; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; TGF-β, transforming growth factor β; TR, thyroid hormone receptor

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Abstract

Hormones are key drivers of cancer development, and alteration of the intratumoral concentration of thyroid hormone (TH) is a common feature of many human neoplasias. Besides the systemic control of TH levels, the expression and activity of deiodinases constitute a major mechanism for the cell-autonomous, prereceptoral control of TH action. The action of deiodinases ensures tight control of TH availability at intracellular level in a time- and tissue-specific manner, and alterations in deiodinase expression are frequent in tumors. Research over the past decades has shown that in cancer cells, a complex and dynamic expression of deiodinases is orchestrated by a network of growth factors, oncogenic proteins, and miRNA. It has become increasingly evident that this fine regulation exposes cancer cells to a dynamic concentration of TH that is functional to stimulate or inhibit various cellular functions. This review summarizes recent advances in the identification of the complex interplay between deiodinases and cancer and how this family of enzymes is relevant in cancer progression. We also discuss whether deiodinase expression could represent a diagnostic tool with which to define tumor staging in cancer treatment or even a therapeutic tool against cancer.

Key Words: thyroid hormone action, deiodinase, cancer, proliferation

Thyroid hormones (THs) are implicated in the control of a variety of biological events including proliferation, apoptosis, differentiation, and metabolism in vertebrates (1, 2). Upon binding with its nuclear receptors (TRs), canonical action of active TH (triiodothyronine [T3]) determines enhancement or inhibition of the expression of target genes. The thyroid gland produces a large excess of the inactive hormone, thyroxine (T4), compared with the active hormone, T3. Thus, most of the circulating T3 and of the T3 intracellular availability derive from the action of 3 enzymes, the iodothyronine deiodinases D1, D2, and D3, that are expressed in a tissue-specific manner in fetal and adult life (3) and selectively catalyze the activation or inactivation of TH. D1 is an integral plasma membrane protein and is mainly expressed in the liver, thyroid, and kidney (4-6). It converts T4 to T3 primarily to provide T3 for the

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circulation and it also works as a scavenger enzyme that recycles iodine to replenish the thyroid's iodine reservoir (3, 6). D2 is an endoplasmic reticulum resident protein expressed in many tissues including muscle, brain, heart, bone, and brown adipose tissue (4, 6, 7). Differently from D1, the main function of D2 is thought to be providing T3 to the nucleus to meet intracellular needs, which is a concept consistent with its subcellular localization (3). D3 is the major TH inactivating enzyme; in fact, it converts T4 and T3 into respectively rT3 and T2, which are inactive at nuclear level. D3 is widely expressed in fetal tissues and placenta, and protects developing tissues from excessive TH levels present in the maternal circulation (8). In adult life, D3 expression declines and persists essentially in skin, brain, and pregnant uterus (9, 10).

It is well established that intracellular regulation of TH concentration is important in cancer, and that this process occurs independently from the systemic control of TH plasma concentration (11). Importantly, different studies suggested that TH plays a crucial role in the neoplastic process. In fact, it has been shown to affect the various phases of tumor formation, growth, and metastasis both in experimental animal models and in humans (12, 13). The first studies to demonstrate a correlation between TH action and cancer date back to the 1980s, and report that TRs are the cellular homologs of v-erbA, which is a viral oncogene product involved in avian erythroblastosis (14, 15). V-erbA is a mutated TRα1 protein that is unable to bind T3 and acts as a dominant negative mutant on the wild-type receptor, thereby attenuating TH signaling. This mutated protein increases its oncogenic potential by cooperating with various oncoproteins to induce tumorigenesis (16).

Subsequently, deregulation of deiodinase expression was identified in diverse tumor contexts. Initial studies, in the late 1980s, showed that immortalized rat pituitary tumor cells (GH4C1) express elevated levels of the D3 enzyme (17). Since then, many in vitro and in vivo studies demonstrated that TH levels vary during the various steps of tumorigenesis, namely tumor formation, growth, migration, and invasiveness, and that the magnitude and specificity of such regulation is tissue and tumor dependent (18-20).

In this review, we focus on the role of deiodinases in the control of TH signaling in cancer. We also discuss the possibility that deiodinases may have diagnostic/therapeutical potential in the cancer field.

D3 and Cancer

Although its expression is barely detectable in adult tissues, the D3 enzyme has been found reactivated in several physiopathological conditions in which cell proliferation is enhanced, as in the case of chronic inflammation, myocardial infarction, tissue repair and critical illness (Fig. 1). In these conditions, D3 expression is increased in order to enable cell function and, in many cases, cell proliferation (21-23). This was demonstrated, in skin and skeletal muscle, to be the consequence of induced proliferation to ensure correct tissue turnover (24). Tissue-specific D3 knockout studies in these models indicate that D3 action is crucial in these conditions (24, 25). Indeed, D3 depletion

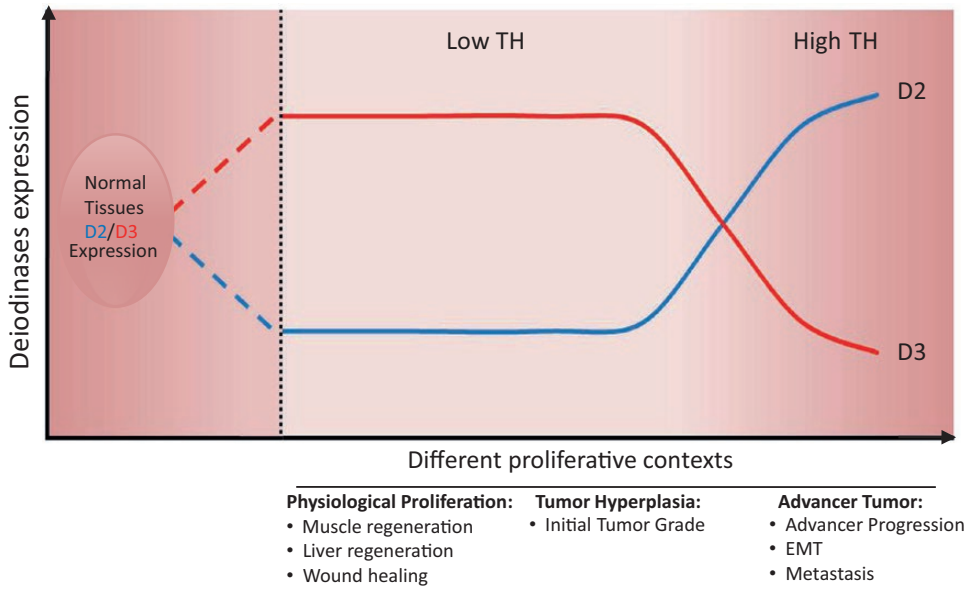

Figure 1. The balance of deiodinase expression under normal conditions, in normal proliferative states and in cancer. Schematic illustration of D2 and D3 expression under various physiopathological conditions. The image shows the most common trend of Dio expression and how it is modified by various stimuli and in various contexts.

in keratinocytes and in myoblasts resulted in drastic decreased cell proliferation and enhanced cell differentiation in keratinocytes (26) and in massive apoptosis of muscle stem cells (24). The mechanisms by which loss of D3 reduce cell proliferation were in both cases due to increased nuclear activity of TH and induction of prodifferentiation and proapoptotic gene expression.

Interestingly, in adult life, D3 is also re-expressed in cancer. D3 was initially identified in various immortalized cell lines derived from adenocarcinoma (HCT116, Caco2, and SW280 cells), breast cancer (MCF-7 cells), endometrium carcinoma (ECC-1), neuroblastoma (SH-SY5Y cells) basal cell carcinoma (BCC), ovarian cancer (HGSO cells), and colon (23, 27-29). Accordingly, D3 is upregulated in many murine and human tumors tissues including the vascular tumors infantile hemangiomas and hepatic hemangioendothelioma (27, 30) as well as in various brain tumors, among which, gliosarcoma and glioblastoma multiforme (31-34). Conversely, D3 was found to be lower in all cases of astrocytoma, irrespective of their grade, than in the normal brain counterpart (31-34). Furthermore, D3 has been detected in pituitary tumors, especially those producing adrenocorticotropic hormone, thyroid-stimulating hormone, or growth hormone, as well as in nonfunctional hormones (35).

Various hormones and other factors, such as estrogens, progesterone, and epidermal and fibroblast growth factors, that promote cell proliferation are potent D3 inducers in a wide variety of cell types. Furthermore, D3 expression in diverse tumoral contexts has been associated to relevant oncogenic pathways namely Shh-Gli2, Wnt/β-catenin, tumor growth factor β (TGF-β) and hypoxia-inducible factor-1α) (11) (Table 1).

Relevant to the understanding of the interplay between deiodinases and cancer is BCC. It is the most common skin cancer and accounts for approximately 80% of all nonmelanoma skin cancers (43, 44). Although its incidence is elevated, it has a low mortality rate (43, 44). The Sonic hedgehog (Shh) pathway is frequently involved and activated in many human tumors including BCC (45). We demonstrated that this pathway affects TH metabolism by a dual convergent mechanism that involves D2 and D3 activity differently. Indeed, we found that Shh induces D3 expression via the binding of Gli2 transcription factor (1 of the Shh effector proteins), to the human DIO3 promoter (21, 46). Furthermore, another Hedgehog family member, Ihh, degrades D2 by inducing WSB-1, which is an E3 ubiquitin ligase adaptor that accelerates D2 degradation (47). These effects exerted on D2 and D3 significantly reduce intracellular T3 concentration. The resulting local cellular hypothyroidism leads to an increase in Cyclin-D1, which in turn results in a sustained proliferative rate (48). Conversely, D3 depletion significantly reduced Cyclin-D1 and proliferation; vice versa when a functional D3 gene is reintroduced in D3-depleted cells, this leads to reincreased Cyclin-D1 levels and cell proliferation. Accordingly, T3 treatment or D3 depletion, in vivo, interferes with tumorigenesis, reducing tumor growth and survival of BCC xenografts in nude mice (21).

MiR21 is an oncomiR that promotes tumor development by inhibiting several tumor suppressor genes and plays a key role in promoting various human and murine

Table 1. Intracellular pathways and main factors that regulate D2 and D3 expression and/or activity in the cancer context

D3 regulators		**Reference**
EGF	↑ upregulated	Hernandez A, *Endocrinology* (1995) (36)
Estrogen	↑ upregulated	Bates JM, *Endocrinology* (1999) (9)
FGF	↑ upregulated	Hernandez A, *Endocrinology* (1995) (36)
GRHL3	↓ downregulated	Di Girolamo D, *J Clin Invest* (2016) (37)
Hypoxia-inducible factor-1α	↑ upregulated	Simonides WS, *J Clin Invest* (2008) (38)
microRNA-21 (miR21)	↑ upregulated	Di Girolamo D, *J Clin Invest* (2016) (37)
Phorbol compounds	↑ upregulated	Courtin F, *J Neurochem* (1991) (39)
Progesteron	↑ upregulated	Bates JM, *Endocrinology* (1999) (9)
Serum	↑ upregulated	Courtin F, *J Neurochem* (1991) (39)
Shh-Gli2	↑ upregulated	Dentice M, *Proc Natl Acad Sci U S A* (2007) (21)
TGF-β	↑ upregulated	Huang SA, *Thyroid* (2005) (10)
Wnt/β-catenin	↑ upregulated	Dentice M, *Gastroenterology* (2012) (23)
D2 regulators		**Reference**
cAMP	↑ upregulated	Wang YY, *Cardiovasc Res* (2010) (40)
NANOG	↑ upregulated	Nappi A, *Cancers* (2020) (41)
NF-κB	↑ upregulated	Zeold A, *Endocrinology* (2006) (42)
Wnt/β-catenin	↓ downregulated	Dentice M, *Gastroenterology* (2012) (23)

tumors including BCC. We recently identified that TH and miR21 reciprocally regulate each other (37). In fact, while TH suppresses miR21 expression, it regulates TH metabolism by indirectly inducing D3 expression in BCC. MiR21 downregulates a tumor suppressor, GRHL3, which is an inhibitor of D3. The novel described functional axis in BCCs, namely the miR21–GRHL3–D3 axis, leads to reduced T3 concentrations in tumor microenvironments thereby favoring tumor growth (37). Conversely, D3 depletion was found to attenuate BCC cell proliferation and in vivo xenograft carcinogenesis, whereas miR21 overexpression enhances the oncogenic potential of BCC cells (46).

D3 overexpression has been detected in early tumorigenesis and its action has been correlated with tumor cell proliferation in colon cancer and in BCC (49). In the intestine, D3 expression has been found to be significantly higher in both adenomas and colon carcinomas than in normal tissues (23). Interestingly, its expression in colon carcinomas is negatively associated with advanced lesion grade. In fact, its expression was found to decrease from G1 to G3, which suggests that D3 is a marker of the early stages of tumorigenesis (23). This finding, which initially appeared counterintuitive and difficult to explain, was subsequently clarified by studies in skin cancer wherein D3 expression declines with cancer progression, and in the more metastatic lesions (see 'D2 and Cancer').

Deiodinases are also involved in the crosstalk between TH and the Wnt/β-catenin pathways (23). Indeed, the Wnt/β-catenin/T-cell factor (TCF) axis transcriptionally induces D3 overexpression and simultaneously represses D2 expression thereby leading to reduced TH signaling in tumors. In the opposite direction, β-catenin knockdown decreases D3 expression while simultaneously increasing D2 expression. Thus, increment of β-catenin signaling leads to D3 upregulation thereby decreasing the intracellular T3 level, and hence its growth-inhibitory effects. Vice versa, active TH can suppress Wnt signaling by inhibiting the β-catenin-TCF4 complex-mediated transcription of Cyclin-D1 in colon cancer (50). In addition, it can regulate the target genes of Wnt signaling by inducing the direct binding of TRs to β-catenin (51). Besides via the Shh and the Wnt pathways, D3 expression is transcriptionally stimulated by TGF-β in hemangioma and glioma cells (52). The local hypothyroidism induced by TGF-β could favor the expression of oncofetal genes and suppress the differentiative effects of TH or promote cell survival in such pathological conditions as cancer (53).

In some cancer cases, very high D3 activity affects plasma TH levels and cause a rare form of hypothyroidism, called "consumptive hypothyroidism" (27). This condition results from the accelerated rate of TH plasmatic degradation, which cannot be compensated for by the production of TH by the thyroid gland.

Overall, the studies available indicate that local attenuation of intracellular T3 occurs in many human tumors, and that this may be advantageous for cell proliferation and tumor growth. An understanding of the molecular basis of upregulated D3 might suggest avenues of research that might lead to new strategies to treat cancer.

D2 and Cancer

D2 expression has rarely been associated with neoplastic transformation. It has been found upregulated in benign hyperfunctioning thyroid nodules and in thyroid tumors including follicular thyroid carcinoma, anaplastic and medullary thyroid cancer (54, 55), whereas its expression was lower in papillary thyroid carcinoma than in normal thyroid tissues (56). This expression pattern is consistent with D2 being a cAMP-responsive gene whose expression increases in those tumoral contexts (thyroid adenoma and follicular carcinoma) in which there is a corresponding overstimulation of the cAMP pathway (Table 1).

At least 2 studies (57, 58) found that functional D2 activity is present in human anterior pituitary tissues, both in adenomas with different secretory activities and in normal tissues. Moreover, Tannahill et al. (35) reported that D2 expression is 2.6-fold higher in pituitary tumors than in normal pituitary tissues, and that the highest D2 expression (3.6-fold) occurred in nonfunctioning pituitary tumors.

Although neurons are thought to be a major target of THs in the brain, the TH-activating enzyme D2, rather than being expressed in the neurons themselves, is expressed in astrocytes and in adjacent glial cells that provide T3 availability in neurons (59). In most brain tumors, D2 expression is remarkably heterogeneous depending on the histological type of the tumor tissue. In fact, D2 expression is lower in astrocytomas and glioblastomas than in the normal counterpart (34) and it is higher in oligodendrogliomas, gliosarcomas, and glioblastoma multiforme (32). Bunevicius et al. (60) evaluated *DIO* polymorphisms in human brain tumors of various histological origin. They identified 5 single nucleotide polymorphisms in the *DIO2* gene (rs225011, rs2267873, rs225015, rs225014, and rs12885300) that commonly occur in glioblastoma patients; however, only the genetic rs12885300 polymorphism was significantly associated with glioblastoma in all samples analyzed. In fact, rs12885300 had a prognostic significance and was associated with an increased mortality risk and 2-year survival.

D2 and D3 are both expressed in normal skin (61-63), suggesting that both activating and inactivating TH enzymes are required to ensure a balanced intracellular level

of TH in the different epithelial skin compartment (64). While the role of D3 has been investigated in the growth and differentiation of keratinocytes (21, 26, 65), both in a pathological and skin cancer context (11, 21, 37, 46, 66), the role of D2 has only recently been partially clarified. Although BCC has been proposed as a paradigm of D3-overexpressing tumor (21, 37, 46), BCC cells and tumors also express D2 (48). Notably, while D2 depletion enhances the proliferative potential of cancer cells, D3 depletion attenuates it. (48).

The role of D2 in skin cancer was further clarified in squamous cell carcinoma (SCC), which, similar to BCC, is a cutaneous cancer caused by keratinocyte transformation (67-69). Unlike BCC, SCC can be invasive and is associated with a substantial risk of metastasis and death (70). During the progression of SCC, D3 and D2 expression are coupled to the various phases of tumorigenesis. Indeed, while D3 is expressed and critical in the early phases of carcinogenesis up to the formation of benign papillomas, D2 is expressed in the late stages of neoplastic transformation, up to the formation of poorly differentiated and invasive SCC. The dynamic expression of D3 and D2 led to the concept that TH attenuation promotes tumor formation and amplification while high T3 levels are later required to ensure the invasiveness and metastatic propensity of cutaneous SCC (20) (Fig. 2). Notably, we reported that the D3 to D2 shift coincides with the EMT transition of SCC cells. Moreover, in the same context, D2 upregulation and the consequent increase in intracellular T3 induced the expression of the pro-EMT gene *Zeb-1* and of its downstream targets Vimentin and N-Cadherin, while reducing the expression of the epithelial markers E-Cadherin and K14 (20) (Fig. 2), thus revealing that D2 is a prognostic marker in cutaneous SCC. Indeed, an analysis of databases deposited in the GEO DataSet Suite, GSE686 (71) and GSE10300 (72), showed that D2 expression is associated with a worse SCC prognosis and correlated with both postsurgical relapse and a shorter disease-free survival. Finally, in SCC and BCC, D2 expression is under the control of the transcriptional factor NANOG (Table 1) (41) which is a marker of stemness and also a pro-oncogenic gene in various epithelial tumors, including SCC (70).

Does D1 Play a Role in Cancer?

D1 expression is often altered in cancer tissues (31). However, the role of D1 in cancer remains largely unexplored, and the studies that are available are in part discordant. In tissues normally expressing D1, such as the thyroid gland, D1 activity has been reported to be either up- or downmodulated in a tumoral context depending on the histological subtype (31, 56).

Meta-analyses of gene expression profiles in human thyroid neoplasia revealed that the *DIO1* gene is underexpressed in both benign and malignant thyroid tumors versus normal tissue (56, 73). Notably, D1 levels were found to be decreased in some histological subtypes of thyroid neoplasms, including papillary thyroid carcinoma and anaplastic thyroid carcinoma, both at various clinical stages (74). By contrast, normal or increased D1 levels were found in follicular thyroid adenoma, follicular thyroid carcinoma, and Hurthle cell cancer versus adjacent normal thyroid tissues (73, 75).

D1 expression was altered also in nonthyroidal cancers (76). Baur et al. (57) provided the first evidence that D1 is expressed in the normal human pituitary gland and in pituitary adenomas, where D1 activity was found to be higher in about 50% of tumors analyzed than in normal pituitary samples (35). In studies on the clinical significance of DIO1 gene polymorphisms in patients affected by a brain tumor, no D1 activity was found in tumors of the central nervous system (60). Bunevicius et al. (60) demonstrated that a common variant in the C-allele of the *DIO1* gene

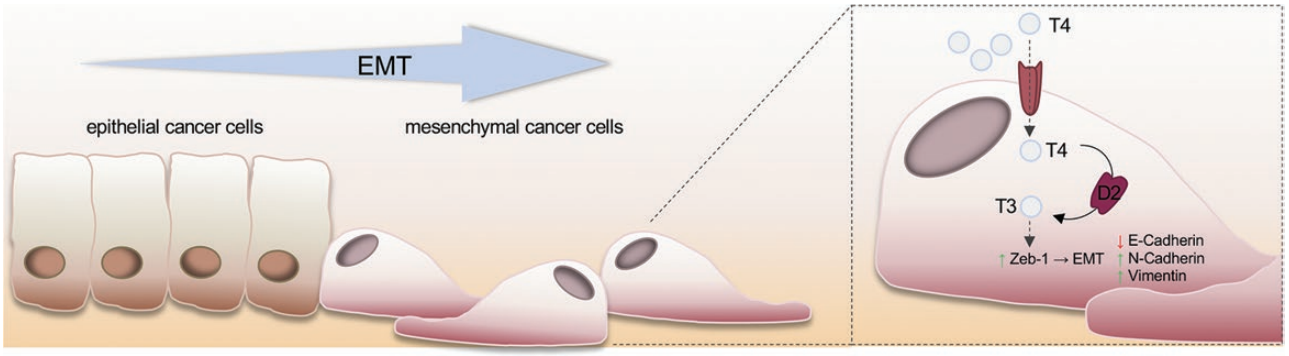

Figure 2. The deiodinase expression profile in cancer cell progression and the mechanism induced by thyroid hormone (TH) to promote the epithelial-to-mesenchymal transition (EMT). Illustration showing the progression of epithelial cancer toward a more aggressive stage and its correlation with an adaptive response of the intracellular TH concentration. The molecular mechanisms by which TH support the EMT are also depicted (right).

Table 2. Variable D1 activity and expression in various cancer settings

Tissue	Type of cancer	D1 activity	Reference
Thyroid	Follicular thyroid adenoma	↑ increased	Schrek R, *J Clin Endocrinol Metab* 1994 (75); Arnaldi LAT, *Thyroid* 2005 (56); de Souza Meyer EL 2005 (73)
	Follicular thyroid carcinoma	↑ increased	Souza Meyer EL, *Clin Endocrinol* 2005 (73) Arnaldi LAT, *Thyroid* 2005 (56)
	Hurthle cell cancer	↑ increased	Souza Meyer EL, *Clin Endocrinol* 2005 (73)
	Papillary thyroid carcinoma	↓ decreased	Murakami M, *J Clin Endocrinol Metab* 2000 (34) Souza Meyer EL, *Clin Endocrinol* 2005 (73) Arnaldi LAT, *Thyroid* 2005 (56)
	Anaplastic thyroid carcinoma	↑ increased	Casula S, *Front Endocrinol* 2012 (31)
Pituitary gland	Pituitary adenoma	↑ increased	Tannahill LA, *Clin Endocrinol* 2002 (35) Baur A, *Eur J Endocrinol* 2002 (57)
Brain	Glioma	not detected	—
	Astrocytoma	not detected	—
	Glioblastoma	not detected	—
	Oligodendroglioma	not detected	—
	Astrocytoma	not detected	—
	Gliosarcoma	not detected	—
	Glioblastoma multiforme	not detected	—
Kidney	Clear cell renal adenocarcinoma	↓ decreased	Pachucki J, *J Endocrinol Invest* 2001 (77)
Liver	Liver adenocarcinoma	↓ decreased	Sabatino L, *Life Sci* 2000 (78)
Lung	Squamous cell lung carcinoma	↓ decreased	Wawrzynska L, *Monaldi Arch Chest Dis* 2003 (79)
Prostate	Prostate cancer	↓ decreased	Dutkiewicz S, *Int Urol Nephrol* 1995 (80)

(rs2235544) reflects increased D1 activity and has a prognostic significance in glioblastoma patients where it is associated with overall survival.

Similar evidence of altered D1 expression has been found in clear cell renal adenocarcinoma (77), liver adenocarcinoma (78), squamous cell lung carcinoma (79), and prostate cancer (80) in which a remarkable reduction (versus normal tissue) or even no D1 activity was found (77, 81). In renal cancer cells loss of D1 seems to contribute to the carcinogenic process since restoration of D1 activity by ectopically DIO1 induction strongly inhibits the expression of genes and proteins involved in proliferation, migration and tumor progression (82, 83). Piekielko et al. identified various DIO1 splicing transcript variants that are specific to cancerous renal tissue and may thus serve as prognostic markers of kidney carcinogenesis (84). DIO1 is also regulated through a post-transcriptional mechanism by miR-224 and miR-383 (85). Downregulation of endogenous DIO1 expression due to overexpression of both miR-224 and miR-383 in clear cell renal cell carcinoma results in decreased intratumoral T3 concentration, which suggests that hypothyroidism may influence and, in particular promote, tumor growth (85).

Low D1 levels were also detected in gastric cancer in which mechanistic studies found that reduced DIO expression was related to selenium deficiency (86, 87). The impairment of DIO1 gene expression in gastric cancer suggests this selenoprotein plays a role in specific subgroups of gastric cancer in humans (88). D1 overexpression has been detected in mammary gland carcinoma (89), at levels at least 2 orders higher than that of intact mammary gland. Moreover, in mammary carcinoma, D1 expression was higher in the early phases than in the late phase of tumorigenesis. In mammary carcinoma, D1 was differentially expressed during tumor progression. In fact, D1 expression was higher in the early phases than in late phases of tumorigenesis (89-91). These results suggest that a progressive loss of D1 activity occurs during tumor progression, and also highlights that D1 expression could be associated with the loss of epithelial differentiation in breast cancer cells (92). Taken together, these studies show that D1 expression is highly heterogeneous in cancer (Table 2). Overall, in multiple tumoral contexts D1 acts like a typical differentiation marker in various tissues (eg, liver, kidney, brain) the expression of which is altered upon neoplastic transformation. Whether those variations are functionally relevant for tumors remains to be investigated.

Conclusions

Research over the past 3 decades has challenged the concept that the central regulation of TH action is the principal cue determining TH availability in target cells. Not only do deiodinases allow tissue-specific modulation of

TH intracellular signaling, but they are also dynamically exploited by target cells to achieve the optimal time- and spatiospecific TH concentration at intracellular level. This is true in physiological contexts as well as during embryonic development and tissue regeneration, and also in such pathological states as tumorigenesis (Fig. 1). Cancer cells are an example of cells that can finely tune TH concentration during the various stages of cancer progression. In skin models, early-stage tumorigenesis requires a high degree of proliferation and is sensitive to TH-mediated cell cycle arrest. To overcome this, cells have devised a strategy enabling attenuation of the TH signal mediated by the D3 enzyme that enables cells to proliferate. Conversely, progression to the invasive and prometastatic stages occurs through upregulation of the TH signal that is induced by the catalytic activity of D2. Why this occurs remains to the established. We have yet to define the events that determine the switch in the D3-D2 deiodinase expression during tumor progression in some cancers. Furthermore, is the switch of deiodinase expression a marker of mutated grading of a tumor? In other words, could the deiodinase profile serve as a marker of tumor staging/grading? This is still an open issue, although the correlations arising from the analysis of large in silico data sets between D2 expression and poor prognosis in skin cancer and reduced D3 expression and lower survival rates in breast cancer support this possibility (93).

Another important issue is the crosstalk between cancer cells and cells that constitute their microenvironment. While the role and significance of deiodinases in cancer cells is starting to be elucidated, the role of the tumor microenvironment in the control of "local" TH concentration is far from being established. It is reasonable that the regulation of intracellular TH concentration in the cells surrounding the tumor will also affect cancer growth and progression.

In this scenario, the finding that deiodinase manipulation in animal models potently affects tumor formation and progression opens the way to the therapeutic application of deiodinase modulators in cancer. Although the druggable control of specific deiodinase action in specific cells remains a mirage, the requirement of deiodinases to allow tumor maintenance may be an Achilles heel for tumor growth. Should this be the case, it may open new avenues of translational research at the crossroads between TH and cancer research fields.

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Additional Information

Correspondence: Domenico Salvatore, Department of Public Health, University of Naples "Federico II", Napoli, Italy. Email: domsalva@unina.it.

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