Translational implications of nongenomic actions of thyroid hormone initiated at its integrin receptor

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THE IDENTIFICATION OF A PLASMA MEMBRANE RECEPTOR for thyroid hormone analogs on integrin αβ3 in 2005 (4) has enabled recognition of several novel cellular actions of the hormone and segregation of effects of thyroid hormone into those initiated at the integrin and actions that begin inside the cell. The latter are primarily well-characterized genomic effects that largely involve nuclear thyroid hormone receptor (TR) isoforms and gene transcription (51, 56). However, other intracellular actions that are nongenomic in origin and begin in cytoplasm (43, 47), at the endoplasmic reticulum (1, 58), and at the mitochondrion (8, 39) have been described. The state of the actin cytoskeleton is also regulated nongenomically by thyroid hormone (13). Nongenomic effects within the cell may culminate in gene transcription, as may those that start at the integrin receptor; hence, a clear distinction between nongenomic and genomic effects of iodothyronines may no longer be practical.

Integrin αβ3, the Thyroid Hormone Plasma Membrane Receptor

Levels of thyroid hormone in the circulation and in tissues of the intact organism are relatively stable. Therefore, cellular actions of the hormone that are initiated at the plasma membrane or inside the cell are in fact steady state. The actions may be seen to be rate-setting for the nongenomic or genomic processes to which they are relevant. The actions of the hormone that are initiated at the integrin receptor are distinct because of the distribution of integrin αβ3. The integrin is concentrated largely in plasma membranes of endothelial cells, vascular smooth muscle cells, cancer cells, osteoclasts (67). The integrin is an attractive target of attempts to manipulate tumor cell proliferation, tumor-related neovascularization, and angiogenesis unrelated to cancer (7). Unrelated to cancer, angiogenesis may be pathological, e.g., in certain retinopathies, or it may be desirable in the context of ischemic tissues. Expression of a TR on αβ3 of osteoclasts appears to underlie a model of thyroid hormone-induced bone mass loss in the mouse (3, 67) or rat (23). The integrin is displayed to a lesser extent on other cells, e.g., muscle cells (59), and on platelets (26), and specific thyroid hormone analogs have been shown to induce human platelet aggregation in vitro (44). Actions of thyroid hormone [L-thyroxine (T4) and 3,3',5-triiodo-L-thyronine (T3)] on the integrin receptor have been readily demonstrated in blood vessels (4, 11, 45, 47) and in studies of tumor cell proliferation (35, 60), whereas immobilized noncancer cells such as CV-1 (monkey kidney) and 293T (human embryonic kidney) have not shown a nongenomic, integrin-dependent, proliferative response to thyroid hormone (Lin HY and Davis PJ, unpublished observations).
Integrins are heterodimeric structural proteins of the plasma membrane that interact with a large number of extracellular matrix proteins, growth factors, and hormones and transduce these interactions or signals into complex cellular events (2, 22, 52). There are more than 20 integrins known, and integrin αvβ3 is one of the most thoroughly investigated. Several integrins, including αvβ3, bear an Arg-Gly-Asp (RGD) recognition site (2, 22, 52) that is critical to the binding elsewhere on the molecule of the extracellular matrix protein ligands that contain this amino acid sequence or its palindrome.

Additional Integrin αvβ3 Ligands

Until recently, it was not clear that a small molecule could serve as a ligand for αvβ3. It is now known that receptors exist on this integrin for a stilbene (34) and for dihydrotestosterone (38) as well as for thyroid hormone (4). Each of these receptors is located at or near the RGD recognition domain on αvβ3. The specific ligands for each of these three receptors do not compete for the other small molecule receptors. Transduction of these different ligand signals at their discrete receptors may nonetheless utilize some of the same signal transducing kinases (4, 34, 40, 41), and they have complex downstream consequences that are distinct or may overlap. For example, T4 can block the p53-dependent proapoptotic activity of resveratrol by disrupting an extracellular signal-regulated kinase 1/2 (ERK1/2)-nucleoprotein complex; inhibition of T4 binding at the cell surface receptor restores the apoptotic action of resveratrol (35).

Binding by the Integrin of Thyroid Hormone and Analogs

A number of features of the receptor on integrin αvβ3 have been characterized. Receptor affinity for T4 is sufficiently high to assure binding of this ligand under physiological conditions (4) (Fig. 1). The affinity for T3 is lower than that for T4. Downstream consequences of hormone binding to the integrin receptor were initially apparent in terms of activation of signal-transducing mitogen-activated protein kinase (MAPK, ERK1/2) and enhancement of angiogenesis (4, 11, 45, 47). This observation permitted description of the site as a receptor. A deaminated analog of T4, tetraiodothyroacetic acid (tetrac), displaces T4 and T3 from the receptor domain but does not mimic the agonist functions of T4 and T3. Thus, tetrac is a specific inhibitor of thyroid hormone (T4 and T3) at the integrin site and may be used in other models of thyroid hormone action to determine whether there is participation of the integrin receptor in such effects. Distinct from its capacity to inhibit binding of T4 and T3 to the integrin, tetrac in the integrin initiates a panel of effects on gene expression in cancer cells and may block actions of endogenous proangiogenic polypeptides. These actions are described below. RGD peptides are partial agonists of T4 and T3 at the thyroid hormone-binding site, and monoclonal antibody to integrin αvβ3 inhibits the plasma membrane activity of T4 and T3. Our studies of tumor cell membrane binding of radioiodinated thyroid hormone have disclosed the presence of no proteins other than the integrin as hormone receptors.

Presence of Two Binding Sites for Thyroid Hormone on Integrin αvβ3

It was initially assumed that the integrin receptor for iodothyronines at or near the RGD recognition domain consisted of a single site that was capable of binding T4, T3, tetrac, and other analogs such as GC-1 (45) and diiodothyropionic acid (DITPA) (47). However, mathematical modeling of the kinetics of binding of hormone to the integrin and comparison of the actions of inhibitors such as tetrac and RGD peptides on integrin-mediated hormone actions have suggested that the hormone-binding domain includes two sites (Fig. 2) (37). One site binds T3 exclusively and transduces the hormone signal by the phosphatidylinositol 3-kinase (PI3K) pathway into cytoplasm-to-nucleus shuttling of TRα1 and into transcription of the hypoxia-inducible factor-1α (HIF-1α) gene. The second site binds both T3 and T4. Here, ERK1/2 transduces the iodothyronine signal into proliferation of tumor cells that express the integrin and into cytoplasm-to-nucleus translocation of TRβ1. Tetrac blocks all of the actions of agonist thyroid hormone analogs at the hormone-binding domain, i.e., both the T3 site and the T4/T3 site. In contrast, an RGD peptide fully inhibits T3 actions mediated by PI3K and does not affect T3

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actions that depend upon ERK1/2, including cell proliferation (37). Thus, tetrac is not an RGD mimic but has a variety of distinctive actions that will be described below.

Other investigators have reported that T3 can nongenomically induce expression of HIF-1α but have presented evidence that the hormone action is initiated in cytoplasm by interaction of T3 with TRβ1 that is resident in this extranuclear compartment (43). The PI3K/protein kinase B/Akt signaling pathway is involved. The complex of TRβ1 and T3 in cytoplasm may also nongenomically initiate a process that ends in transcription of the Na⁺-K⁺-ATPase gene and insertion of the gene product into the plasma membrane (32).

Proximity and Cross-Talk Between Integrin αvβ3 and Growth Factor Receptors

The topography of the integrin and certain proteins clustered with it can be inferred from several studies. For example, the functions of the epidermal growth factor receptor (EGFR) are refined by thyroid hormone, including potentiation of the effect of EGFR on tumor cell proliferation; tetrac inhibits these actions, implying the existence of cross-talk between the integrin receptor and the EGFR (58). Co-clustering and interdependence of EGFR and integrin αvβ3 have been well described by others (40), but not as a function of thyroid hormone action. Bidirectional cross-talk between the vascular endothelial growth factor (VEGF) receptor and the β3 integrin has been reported (41). The proangiogenic action of thyroid hormone analogs (11, 45, 47), as noted above, is mediated by the integrin receptor for the hormone (4) and is inhibited by tetrac. Interestingly, tetrac blocks the actions of VEGF and of basic fibroblast growth factor (bFGF) in several models of angiogenesis (48) in the absence of thyroid hormone. These observations infer the existence of cross-talk between the integrin receptor for thyroid hormone and the VEGF and bFGF receptors.

Translational Implications of Nongenomic Actions of Thyroid Hormone Initiated at Integrin αvβ3

Thyroid hormone and angiogenesis. That thyroid hormone analogs have angiogenic activity has been shown in rodent heart by Tomanek et al. (61) and Zheng et al. (71), in the heart and brain by Kuzman and colleagues (28, 29), Schlenker et al. (57), Davis et al. (12), El Eter et al. (14), and Mousa and colleagues (45, 47), and in several model systems by Bergh et al. (4). Tomanek et al. (61) implicated bFGF in the hormone-induced blood vessel response, but the initiation site of hormone action in the cells involved was not clear, and relatively high T4 doses were used. Kuzman and colleagues (28, 29) have shown that agonist thyroid hormone (thyromimetic) analogs are proangiogenic in the postinfarcted hamster heart by a pathway that involves Akt signaling. Thyroid hormone also has substantial proangiogenic activity on brain blood vessels (57). Angiogenic activity of iodothyronine analogs that is initiated at the integrin receptor has been demonstrated in the blood vessels of the chick chorioallantoic membrane (CAM) model (11, 45, 47) and the human dermal microvascular endothelial cell (HDMEC) sprouting model (46). This hormonal activity requires ERK1/2 activation. The effect is blocked by monoclonal integrin αvβ3 antibody (Fig. 3), by tetrac (Fig. 4), and by pharmacological inhibition of the ERK pathway (11). Integrin-originated angiogenic activity may involve increased bFGF expression and bFGF release (11) and autocrine action of this growth factor on endothelial cells, but other vascular growth factors may also be involved. Proangiogenic thyroid hormone analogs include T4, T3, and, in several models (47), DITPA. As pointed out above, the integrin receptor can distinguish between T4 and T3. Some expression of the integrin on human platelets allows the latter to be activated and agglutinated by T4 but not by T3 or DITPA (44). T3 and DITPA are thus more attractive proangiogenic agents in the context of experimental organ or limb ischemia when platelet agglutination is undesirable. Nonetheless, both DITPA and T4 have been tested experimentally in a rabbit hindlimb model of ischemia and have been shown to increase blood vessel buds and the number of capillaries/muscle fiber in the treated limb (14). In the setting of wound-healing models, the testing of T4 is appropriate because coagulation is an asset, but Safer et al. (56) have demonstrated in an intact animal model that T3 is an effective promoter of wound healing.

Antiangiogenesis and tetrac. There are several clinical settings in which inhibition of angiogenesis is desirable. These include retinal neovascularization, the vascular supply of cancers, primary blood vessel tumors, e.g., hemangioma, and certain erythematous clinical conditions of the skin, such as rosacea. VEGF is a host factor that is engaged in the pathogenesis of most of these conditions (14, 56), but more than one
vascular growth factor may be involved pathogenetically. Thus, a treatment strategy directed at a single proangiogenic agent is unlikely to be optimal. Via the integrin receptor, ambient thyroid hormone levels in the intact host may be supporting exuberant angiogenesis (6) in the settings cited above, regardless of the primary cause(s) of the lesions. The hormonal effect may be a direct one on endothelial or vascular smooth muscle cells, or it may be indirect through interactions with mechanisms of release of vascular growth factor or potentiation of their actions at their own (growth factor) cell surface receptors. EGF is also a proangiogenic factor, and, as noted above, thyroid hormone can potentiate certain actions of this factor at the EGFR (58).

The concept that the action of tetrac at the integrin αvβ3 receptor was limited to inhibition of the binding of agonist thyroid hormone analogs was shown to be erroneous when tetrac actions were studied in the absence of thyroid hormone. In both the CAM and HDMEC three-dimensional sprouting assays (48), for example, tetrac inhibited the actions of VEGF and bFGF in the absence of thyromimetic thyroid hormone analogs. We show in Fig. 5 the results of unpublished studies related to Ref. 48 in which tetrac nanoparticles inhibited the proangiogenic activity of bFGF in the CAM angiogenesis model. Reformulated as a nanoparticle, tetrac that is stably bonded to the surface of the particle is more potent than unmodified tetrac in reducing cancer xenograft vascularity (64). Nanoparticulate tetrac cannot gain access to the cell interior and is exclusively a thyroid hormone antagonist at the integrin. This feature of exclusion is desirable, since unmodified tetrac within the cell has low-grade, but appreciable, thyromimetic activity (30).

In addition to blocking via the integrin the proangiogenic actions of T4 and T3 and of VEGF and bFGF, tetrac coherently acts at this site to affect another dimension of new blood vessel formation. Angiopoietin (Ang)-2 is a protein that destabilizes the structure of established blood vessels as a preparatory step in angiogenesis. Tetrac inhibits expression of the Ang-2 gene (48). However, there is no effect of tetrac on Ang-1, whose gene product stabilizes blood vessel structure.

Thyroid hormone analogs and proliferation of tumor cells. The integrin receptor-based proliferative activity of agonist thyroid hormone analogs has been described in a number of human (6, 17, 18, 35, 60) and animal (12) cancer cell lines. The mechanisms involved are not clear. The possibility of clinically undesirable contributions of normal circulating levels of thyroid hormone to existing tumor cell proliferation has been raised (12, 18, 31, 36, 70) and clinical hypothyroidism has been reported to have desirable actions on end-stage glioblastoma (20), on breast cancer (9), and possibly on head-and-neck cancer (50). The clinical studies on breast cancer and head-and-neck tumors were retrospective and relied upon the coin-

Fig. 3. Proangiogenic action of T4 demonstrated in the chick chorioallantoic membrane (CAM) model. Physiological total T4 concentration (10⁻⁷ M) added to the CAM model induced neovascularization, shown here at 3 days. Blood vessel branch points were counted in triplicate CAM preparations from each of the 3 experiments. Representative figures and the accompanying table depict the T4 effect. A monoclonal antibody to integrin αvβ3 (LM609) inhibited the effect of the hormone on angiogenesis. Propylthiouracil was present in all samples to inhibit 5'-deiodination of T4 to yield T3. This figure is reproduced from Ref. 4 with permission from the publisher.

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Inhibitory effect of αvβ3 MAB (LM609) on T₄-stimulated angiogenesis in the CAM model

<table>
<thead>
<tr>
<th>CAM Treatment</th>
<th># of branch points ± SEM</th>
</tr>
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<tbody>
<tr>
<td>PBS</td>
<td>73 ± 8</td>
</tr>
<tr>
<td>T₄ (0.1 μM)</td>
<td>170 ± 16</td>
</tr>
<tr>
<td>T₄ + LM609 (10 μg)</td>
<td>109 ± 9</td>
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Fig. 4. Effect of tetrac on induction of angiogenesis in the CAM model by T₄ and T₄-agarose. T₄ covalently bound to agarose is excluded from the cell interior. Unmodified T₄ and T₄-agarose stimulated angiogenesis equally well, thus implicating the plasma membrane as the site of initiation of the hormonal effect. Tetrac inhibited the angiogenic activity of both T₄ and T₄-agarose. Permission for reproduction of this figure from Ref. 11 was provided by the publisher.
Thyroid hormone is a growth factor for human thyroid carcinoma cells in vitro (35). This effect is mediated by the integrin receptor. If this scenario is the case clinically, then it poses a special problem, since thyroid hormone in greater-than-replacement dosage is used in thyroid cancer patients to suppress endogenous thyrotropin (TSH) secretion by the pituitary gland. That is, differentiated thyroid cancers are conventionally viewed as TSH dependent. There is no question that TSH is an important growth factor for such cancers. However, in the thyroid cancer patient in whom the cancer recurs despite full suppression of endogenous TSH, thyroid hormone dependence and TSH independence of the relapsed lesion may be postulated.

Iodothyronines cause human breast cancer cells to proliferate in vitro by a mechanism that mimics that of 17β-estradiol (Fig. 8) (60). That is, estrogen and thyroid hormone both stimulate MAPK-mediated phosphorylation of the nuclear estrogen receptor-α (ERα) at Ser118 in human breast cancer (MCF-7) cells. This nuclear receptor activation step is required for stimulation by estrogen of tumor cell proliferation and is
Thyroid hormone is discussed here solely as a proliferative agent for existing tumor cells. Integrin αvβ3 is concentrated, as noted above, in plasma membranes of cancer cells, endothelial cells, vascular smooth muscle cells, and osteoclasts. We have noted above that thyroid hormone is not a growth factor for immortalized noncancer cells.

Reproduced in the absence of estrogen by T4 and by T4-agarose that does not gain entry to the interior of the cell. Pharmacological reduction of the amount of functional ER in MCF-7 cells by treatment with ICI 182,780 decreased the effect of T4 on Bcl-Xs by competing with tetrac for the integrin receptor site. These data were reproduced from Ref. 36 with permission from the publisher.

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Fig. 7. Accumulation of proapoptotic Bcl-Xs protein in tetrac-treated human glioblastoma U87MG cells. The cells were treated with T4, tetrac, or both (each at total concentrations of 10^{-7} M) for 48 h. Harvested cytosolic proteins from each sample were separated by gel electrophoresis and immunoblotted for proapoptotic Bcl-Xs (5) or antiapoptotic Bcl-Xl. Alone, T4 did not affect accumulation of Bcl-Xs, but T4 partially inhibited the action of tetrac on Bcl-Xs by competing with tetrac for the integrin receptor site. These data were reproduced from Ref. 36 with permission from the publisher.

Fig. 8. Proliferation of human breast cancer (MCF-7) cells induced by thyroid hormone (T4) or 17β-estradiol (E2). MCF-7 cells are nuclear estrogen receptor-α (ERα)-positive. T4 total and free concentrations, respectively, were 10^{-7} and 10^{-10} M in the cell culture system. Cell proliferation was quantitated by [3H]thymidine uptake. Thyroid hormone and E2 were both effective stimulators of MCF-7 cell proliferation. The ER inhibitor ICI 182,780 (ICI) antagonized the effect of E2, as expected, and that of thyroid hormone. Thus, stimulation of proliferation of these breast cancer cells by T4 is ER mediated. Additional studies have shown that T4 stimulates specific serine phosphorylation of ERα compared with E2 (60). This figure was reproduced from Ref. 60 with permission from the publisher.

Fig. 9. Summary of actions of thyroid hormone analogs nongenomically initiated at the plasma membrane or in cytoplasm. Such actions may culminate in complex, nucleus-mediated cellular events. 1) T3 may act at integrin αvβ3 receptor to activate ERK1/2 via phospholipase C (PLC) and protein kinase C (PKCα). Among the consequences of ERK1/2 activation are specific serine phosphorylation of the cytoplasmic/nuclear TRβ1, ERα, and signal transducers and activators of transcription STAT1α and STAT3 (13). When residing in cytoplasm, these proteins are shuttled to the nucleus under the nongenomic direction of thyroid hormone, where the proteins are transcriptionally active and may modulate the actions of certain cytokines and growth factors. T4-activated ERK1/2 also mediates the actions of the hormone on tumor cell proliferation (12, 35, 36) and on angiogenesis (4, 11). 2) T4 and reverse T3 (rT3) bind to the truncated thyroid hormone receptor TRα1 in cytoplasm to cause actin polymerization (13) that is critical to cell motility and other functions. 3) T4 activates PI3K, either by a cytoplasmic mechanism (32, 43) or via plasma membrane integrin αvβ3 (37), to cause transcription of the HIF-1α gene (37, 42) and other genes or shuttling of cytoplasmic TRα1 to the cell nucleus (37). Cytosolic TRβ1 and PI3K are involved in stimulation by T3 of the activity of Na^+/K^-ATPase (32, 33) and of other life cycle features of the sodium pump (gene expression, plasma membrane insertion). Tetrac is an analog of T4 that inhibits binding of T4 and T3 to the TR on integrin αvβ3 and thus blocks the actions of agonist thyroid hormone analogs on cancer cell proliferation and on angiogenesis. 4) Covalently bonded to a nanoparticle (NP), tetrac NP acts exclusively at the cell surface thyroid hormone integrin receptor and by not entering the cell is unable to express low-grade, nucleus-mediated thyromimetic activity that the unmodified molecule possesses (30). Acting at the cell surface receptor and in the absence of T4 and T3, tetrac may also affect gene expression in cancer cells (16). These include thrombospondin (THBS1), caspase-2 (CASP2), and CYB1.
Radiosensitization of cancer cells. Recent in vitro studies have revealed that exposure of rodent glioma cells to unmodified tetrac is radiosensitizing (19). A one-hour exposure to tetrac is sufficient to induce sensitization to immediate radiation exposure, and the integrin receptor has been proposed to mediate the drug effect (19). The molecular basis of this action of the thyroid hormone analog is not yet clear. The radiosensitization phenomenon awaits confirmation in other tumor cell lines. The reciprocal possibility that physiological concentrations of agonist thyroid hormone analogs, in contrast to tetrac, may confer some degree of radio resistance has not been investigated.

Retention by tumor cells of cancer chemotherapeutic agents. Mechanisms of cancer cell resistance to chemotherapeutic agents include decreased cell retention time of the agents. Export of the agents may relate to the existence in the plasma membrane of multidrug resistance (MDR; P-glycoprotein) pumps (1, 27). Studied in doxorubicin-resistant human breast cancer (MCF-7) cells, treatment with tetrac results in importantly prolonged intracellular residence time of radiolabeled doxorubicin (54). The integrin receptor is implicated in this phenomenon, but the molecular mechanism is unclear. Tetrac does not affect the cellular abundance of P-glycoprotein in these cells (54). Thyroid hormone is known via αvβ3 to modulate the activity of several ion transport systems in the plasma membrane, including the Na+/H+ exchanger (10), Na+/K+-ATPase (33), Ca2+-ATPase (49, 63), and Na+ current (68), but it is not yet known whether the hormone directly affects the activity of MDR pumps. The linear relationship between intracellular pH and doxorubicin efflux (55) suggests that inhibition by tetrac of Na+/H+ exchanger activity and consequent acidification could adversely affect MDR pump action. Whatever the mechanism that underlies increased tumor cell retention of doxorubicin, the effect is desirable in resistant cells. Retention times of other chemotherapeutic agents in other cancer cell types exposed to tetrac have not been determined.

Conclusions

The molecular basis for actions of thyroid hormone analogs that are nongenomic in origin are summarized in Fig. 9. Several translational implications for tumor cell biology are apparent from modulation by tetrac of the activity of the thyroid hormone receptor on integrin αvβ3. Acting via this receptor, the hormone analog has unexpected and attractive inhibitory actions on cancer proliferation and on tumor xeno-graft angiogenesis. Tetrac also has radiosensitizing effects and effects on tumor cell line retention of a conventional chemotherapeutic agent that require additional examination.

The extraordinary functions of the integrin in transducing signals generated by extracellular proteins and small molecules into a variety of distinctive cellular events help explain the ability of tetrac to affect multiple functions in the cancer cell. Were the integrin generously represented on the surfaces of all cells in the intact organism, then a disruptive toxicity profile for tetrac would be inevitable. However, substantial expression of αvβ3 on a wide variety of cancer cells and on tumor-related vasculature that turns over rapidly makes the integrin an attractive target. The integrin hormone receptor has several novel features. These include subspecialization of the ligand-binding domain so that functions regulated from that domain are distinguished from those of RGD recognition site ligands. The receptor domain distinguishes among thyroid hormone analogs in terms of function as well as affinity. It has been possible to reformulate thyroid hormone analogs into agents that act exclusively at the integrin receptor and are excluded from the interior of the cell. That is, these formulations do not have access to classical nuclear receptors for the hormone or to other proteins that may mediate idothyronine actions on cellular organelles.

The integrin receptor for thyroid hormone also offers the prospect of selective pro- and antiangiogenesis intervention in the absence of tumor. The clinical settings here in patients include proliferative retinopathy, where tetrac-induced antiangiogenesis is desirable, and T3- or DITPA-induced neovascularization in the context of ischemia.

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REFERENCES

9. Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patanjgan M, Hsu L, Krishnamurthy S, Theriault RL, Hortobagyi GN. Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. Cancer 103: 1122–1128, 2005.

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a cell surface receptor, thyroid hormone is a growth factor for glioma cells. Cancer Res 66: 7270–7275, 2006.
37. Mousa SA, O’Connor LJ, Davis FB, Davis PJ. Pro-angiogenesis action of the thyroid hormone analog 3,5,3,5-diiodothyropropionic acid (DITPA) is initiated at the cell surface and is integrin mediated. Endocrinology 147: 1602–1607, 2006.


