

Nanotetrac targets integrin $\alpha v \beta 3$ on tumor cells to disorder cell defense pathways and block angiogenesis

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Abstract: The extracellular domain of integrin $\alpha v \beta 3$ contains a receptor for thyroid hormone and hormone analogs. The integrin is amply expressed by tumor cells and dividing blood vessel cells. The proangiogenic properties of thyroid hormone and the capacity of the hormone to promote cancer cell proliferation are functions regulated nongenomically by the hormone receptor on $\alpha v \beta 3$. An L-thyroxine (T_4) analog, tetraiodothyroacetic acid (tetrac), blocks binding of T_4 and 3,5,3'-triiodo-L-thyronine (T_3) by $\alpha v \beta 3$ and inhibits angiogenic activity of thyroid hormone. Covalently bound to a 200 nm nanoparticle that limits its activity to the cell exterior, tetrac reformulated as Nanotetrac has additional effects mediated by $\alpha v \beta 3$ beyond the inhibition of binding of T_4 and T_3 to the integrin. These actions of Nanotetrac include disruption of transcription of cell survival pathway genes, promotion of apoptosis by multiple mechanisms, and interruption of repair of double-strand deoxyribonucleic acid breaks caused by irradiation of cells. Among the genes whose expression is suppressed by Nanotetrac are *EGFR*, *VEGFA*, multiple cyclins, catenins, and multiple cytokines. Nanotetrac has been effective as a chemotherapeutic agent in preclinical studies of human cancer xenografts. The low concentrations of $\alpha v \beta 3$ on the surface of quiescent nonmalignant cells have minimized toxicity of the agent in animal studies.

Keywords: integrin, thyroid hormone, thyroxine, antiangiogenesis, proapoptosis

Introduction

A number of in vitro and in vivo studies have supported a role for thyroid hormone in the proliferation of tumor cells.¹⁻⁷ Thyroid hormone is proangiogenic,⁸⁻¹¹ and this property may be relevant to tumor biology.^{12,13} Clinical evidence of thyroid hormone dependence of cancers has come from studies of glioblastoma,¹⁴ breast cancer,¹⁵ and tyrosine kinase inhibitor-treated renal cell carcinoma,¹⁶ and head and neck cancers.¹⁷ Such studies have been reviewed by Hercbergs et al.¹⁸

In 2005, we described a receptor for thyroid hormone on plasma membrane integrin $\alpha v \beta 3$ that regulated angiogenesis.⁹ Of the more than 20 plasma membrane integrins, only $\alpha v \beta 3$ binds thyroid hormone and hormone analogs such as tetraiodothyroacetic acid (tetrac).⁹ The ectodomains of integrins contain a variety of binding sites for extracellular matrix proteins.¹⁹ On integrin $\alpha v \beta 3$, however, there are also discrete small molecule receptors for resveratrol²⁰ and androgen,²¹ as well as for thyroid hormone. The intracellular domain of the integrin activates signaling pathways that relate to specific gene transcription²² and interacts with the cytoskeleton.²³ The nongenomic regulation of the state of the actin cytoskeleton by L-thyroxine (T_4) described by Leonard and Farwell²⁴ and Farwell et al²⁵ may be mediated by $\alpha v \beta 3$ (see the Angiogenesis modulation by thyroid hormone and tetrac formulations section).

The thyroid hormone receptor on the integrin mediates the actions of the hormone on tumor cell proliferation^{5–7,12,26} and on angiogenesis.^{8,9,12,13} We discuss in this review the significance of the interface of thyroid hormone and cancer cells at integrin $\alpha v\beta 3$, interpreted in part by the actions of the deaminated analog of T_4 , tetrac, and its nanoparticulate formulation as antithyroid agents at the integrin. In this formulation, tetrac is covalently bound to poly(lactic-co-glycolic acid) and thus is excluded from the cell interior.¹¹ Acting exclusively at the integrin, Nanotetrac does block the proliferative and proangiogenic effects of T_4 and 3,5,3'-triiodo-L-thyronine (T_3) initiated at the cell surface. However, the compound also has effects via the integrin on transcription of genes integral to cancer cell survival pathways, and these effects appear unrelated to agonist T_4 and T_3 . The integrin also mediates antiangiogenic actions of Nanotetrac that are independent of T_4 and T_3 . The nanoparticulate drug does not affect genomic actions of thyroid hormone within the cell that depend primarily upon nuclear receptor (TR)– T_3 complex formation²⁷ or interactions of T_3 with mitochondria.²⁸

Thyroid hormone–tetrac receptor on integrin $\alpha v\beta 3$

The thyroid hormone–tetrac binding site on the integrin includes contributions from both αv and $\beta 3$ monomers.²⁹ The site accommodates T_4 , T_3 , tetrac, and other hormone analogs such as diiodothyropropionic acid.³⁰ The affinity of the receptor is higher for T_4 than for T_3 ,⁹ and binding of T_4 occurs at physiological levels of free T_4 . The significance of this is that circulating T_4 supports tumor cell proliferation in the intact organism.

The receptor is subspecialized. One domain that controls cell proliferation binds both T_4 and T_3 and activates the mitogen-activated protein kinase (ERK1/2) signal transduction pathway.³¹ This area of the receptor is involved in stimulation of cell proliferation. The second domain binds only T_3 and activates the phosphatidylinositol 3-kinase pathway. Downstream consequences of such activity include nuclear uptake of TR α resident in cytoplasm and expression of the hypoxia-inducible factor-1 α (*HIF-1 α*) gene.³¹ Tetrac blocks hormone actions initiated at both domains.

Angiogenesis modulation by thyroid hormone and tetrac formulations

The proangiogenic activity of thyroid hormone – and the antiangiogenic properties of tetrac – which begins at $\alpha v\beta 3$, appears to involve several mechanisms. For example, the

integrin is known to interact physically with the vascular endothelial growth factor (VEGF) receptor family that is adjacent to $\alpha v\beta 3$ molecules.³² In the absence of T_4 and T_3 , tetrac and Nanotetrac block activity of VEGF and basic fibroblast growth factor (bFGF) in the chick chorioallantoic membrane angiogenesis assay,³³ presumptively by disrupting crosstalk between the integrin and VEGF receptor and bFGF receptor. However, tetrac can also decrease *bFGF* gene transcription and decrease bFGF protein release by cells.⁸ Agonist thyroid hormone enhances platelet-derived growth factor activity (Mousa, unpublished observations), and this effect is subject to tetrac inhibition. Epidermal growth factor (EGF) is also proangiogenic, and Nanotetrac, acting via $\alpha v\beta 3$, downregulates transcription of the *EGFR* gene.¹² Thus, a number of molecular mechanisms are involved in actions of thyroid hormone analogs at their receptor on the integrin. Other tumor cell genes affected by Nanotetrac via $\alpha v\beta 3$ are discussed here.

Beyond vascular growth factor gene expression and vascular growth receptor function, there are additional contributions to angiogenesis that originate at the thyroid hormone receptor on the integrin. Endothelial cell migration is regulated by T_4 at $\alpha v\beta 3$ and blocked by tetrac,³⁴ as is fibroblast motility. The integrity of the actin cytoskeleton depends upon T_4 – conversion of soluble actin to fibrous actin by a nongenomic mechanism^{24,25} – and cell motility and integrin function depend upon the state of the cytoskeleton. Leonard and Farwell²⁴ have also shown that cell attachment to laminin is T_4 -requiring and integrin-dependent. We propose that the actions of T_4 on the state of actin and cell–laminin interactions may be initiated at $\alpha v\beta 3$. Integrin clustering in response to binding of Arg-Gly-Asp peptides promotes actin polymerization.³⁵ The laminin effect of the hormone is impaired by blockade of recognition sites for such peptides on the integrin. Blockade of such sites can inhibit certain of the actions of iodothyronines at their receptor on the integrin.³¹

Small arteriole muscularization is promoted by thyroid hormone,³⁶ but it is not yet known whether this effect is $\alpha v\beta 3$ -dependent. Tetrac decreases abundance of angiotensin-2 (*Ang-2*) messenger ribonucleic acid (mRNA) in endothelial cells³³ but does not affect *Ang-1*. *Ang-2* protein destabilizes blood vessel structure in anticipation of vascular growth factor action and promotion of angiogenesis, whereas *Ang-1* stabilizes such structure and functionally is antiangiogenic.

The distribution of the integrin among various types of cells is relevant to therapeutic exploitation of the small molecule receptors on $\alpha v\beta 3$, such as those for thyroid hormone. Rapidly dividing cells, notably cancer cells and endothelial

cells about tumors, express the integrin generously. Nonmalignant, quiescent cells do not. When we examined immortalized noncancer human and nonhuman primate cells for susceptibility to antiproliferative action of Nanotetrac, we found no drug activity (Mousa, unpublished observations).

Tumor cell genes whose transcription is regulated by the thyroid hormone–tetrac receptor on integrin $\alpha v \beta 3$

We have identified more than 40 genes in human cancer cells that are regulated from $\alpha v \beta 3$ by Nanotetrac.^{12,37,38} Certain of these genes are presented in Table 1, with the data drawn from studies of MDA-MB-231 breast cancer cells³⁷ and medullary thyroid carcinoma cells.³⁸ What is remarkable is the coherence of the up- or downregulation of these genes. For example, transcription of proapoptosis genes is increased by Nanotetrac – *CASP2*, *CASP8AP2*, *BCL2L14*, *DFFA* – and antiapoptotic *XIAP* expression is decreased. Twenty-one of 23 protooncogenes are downregulated, as are eight of nine cyclin genes that are critical to cell cycle regulation and a cyclin-dependent kinase. All of these drug effects are consistent with a desirable multitarget chemotherapeutic profile. It should also be noted that tetrac/Nanotetrac promotes accumulation of proapoptotic Bcl-X_s mRNA but does not affect Bcl-X_L.³⁹

Table 1 Representative tumor cell genes whose expression is differentially modulated by Nanotetrac (nanoparticulate tetrac)

Function/gene	Up- or downregulation
Cell cycle	
Cyclins	↓
<i>CDKN2C</i>	↑ cyclin-dependent kinase inhibitor
Proapoptosis	
<i>CASP2</i>	↑
<i>CASP8AP2</i>	↑
<i>DFFA</i>	↑ DNA fragmentation factor subunit alpha
<i>BCL2L14</i>	↑
Antiapoptosis	
<i>XIAP</i>	↓ X-linked inhibitor of apoptosis protein
Wnt–catenin pathway	
<i>CTNNA1</i>	↓
<i>CTNNA2</i>	↓
<i>CBY1</i>	↑ nuclear inhibitor of catenin
Angiogenesis	
<i>TSP1</i>	↑
Vascular growth factors	
<i>VEGFA</i>	↓
<i>bFGF</i>	↓
Growth factor receptors	
<i>EGFR</i>	↓

The complex actions of Nanotetrac on angiogenesis have been mentioned previously, and *EGFR* was included in this context. EGF is mitogenic and its receptor mediates other tumor cell support functions beyond angiogenesis. These have made the receptor, EGFR, and its ligand, EGF, chemotherapeutic targets,⁴⁰ and cetuximab is the prototypical clinical EGFR antibody. The action of Nanotetrac to suppress transcription of the EGF receptor gene conceptually has advantages over EGFR antibody because Nanotetrac is targeted to cancer cells that express $\alpha v \beta 3$ and thus does not affect this cell surface target in healthy (nonmalignant) cells. In addition, Nanotetrac has a spectrum of other anticancer actions noted previously.

One of the unique attributes of the tetrac receptor on integrin $\alpha v \beta 3$ is that it is linked to the thrombospondin 1 (*TSP1*; *THBS1*) gene. Expression of this gene is almost invariably suppressed in tumor cells, since the gene product is an endogenous antiangiogenic factor. Nanotetrac causes transcription of *TSP1*, and this is one of a number of antiangiogenic mechanisms activated by the drug. Another important function of the TSP1 protein is that it is a ligand of CD47.⁴¹ CD47 is a cell surface antigen that, expressed by cancer cells, limits antitumor immunity – producing the “Do not eat me” state – and immune system-mediated phagocytosis/destruction.⁴² Antibodies to CD47 are being tested for utility as anticancer agents that promote host immune system attack on cancer cells. Bound to CD47, TSP1 released in response to Nanotetrac may achieve the same chemotherapeutic outcome as anti-CD47.⁴¹

Rae et al⁴³ have shown that matrix metalloproteinase-9 (*MMP-9*) gene expression is increased by thyroid hormone in ovarian cells. Ashur-Fabian has confirmed that T₄ causes transcription of *MMP-9* in myeloma cells and has found that tetrac blocks this effect (Cohen, Flint, Shalev, and Ashur-Fabian, unpublished observations). Thus, $\alpha v \beta 3$ is involved in this effect on *MMP-9*. The significance of the effect is that MMPs act on cell–cell interaction and cell–matrix adhesion proteins, destabilizing tissues and promoting tumor cell invasiveness and metastasis.⁴⁴

Finally, agonist thyroid hormone induces internalization of $\alpha v \beta 3$.⁴⁵ This was initially interpreted by us to reflect the known recycling of the integrin⁴⁶ but is now recognized to be relevant to gene expression. Tetrac blocked internalization of $\alpha v \beta 3$, and we subsequently found that T₄ directed the αv monomer, but not $\beta 3$, into the cell nucleus. In the nucleus, αv was found to function as a coactivator, supporting transcription of several genes that are important to cancer cell biology, including *HIF-1 α* and the estrogen

receptor ($ER\alpha$).⁴⁵ Thus, the thyroid hormone–tetrac receptor on $\alpha v\beta 3$ has a variety of functions mediated by the intact heterodimer, but the interaction of hormone and $\alpha v\beta 3$ is capable of changing the structure and function of the integrin.

Radiosensitization induced by tetrac formulations

Nanotetrac and tetrac induce radiosensitization of cancer cells via the $\alpha v\beta 3$ receptor for thyroid hormone.^{47,48} Our studies of this action disclosed a remarkable behavior of the integrin when tumor cells are subjected to radiation – namely, an acute and substantial increase in the number of active (“open conformation”) $\alpha v\beta 3$ molecules in the plasma membrane.⁴⁹ We interpret this as a defensive response. Nanotetrac blocks this radiation response. The $\alpha v\beta 3$ -dependent radiosensitization process is also associated with a tetrac-induced loss of capacity of tumor cells to repair double-stranded deoxyribonucleic acid breaks caused by radiation.⁴⁸

Discussion

In the course of describing certain novel cellular actions of T_4 and T_3 , we determined that these actions could be reproduced by agarose- T_4 , a nanoparticulate formulation of the hormone that cannot enter the cell.^{8,50,51} Thus, the actions were necessarily initiated at the plasma membrane and were nongenomic in mechanism. We also found that tetrac, the naturally occurring deaminated metabolic product of T_4 , inhibited these membrane-initiated actions of iodothyronines and agarose- T_4 .^{50,51} We described the plasma membrane receptor for thyroid hormone on integrin $\alpha v\beta 3$ a decade ago⁹ and distinguished the downstream consequences and mechanisms of nongenomic actions initiated at the integrin from genomic actions.^{12,27} We confirmed the activity of tetrac as an inhibitor of nongenomic actions of T_4 and T_3 at the hormone receptor on $\alpha v\beta 3$.^{9,12} Reformulation of tetrac as Nanotetrac^{38,52} resulted in an agent that is limited to the extracellular space and that is a more potent inhibitor of agonist thyroid hormone actions.¹² In addition, as pointed out, Nanotetrac modulates expression of a broader spectrum of cancer cell survival pathway genes.

Nanotetrac has an attractive set of properties as an anticancer and antiangiogenic agent.¹² The $\alpha v\beta 3$ integrin that contains the specific target of Nanotetrac is expressed by, or activated primarily on, cancer cells and supporting blood vessels about tumors. This limits the risk of exposure of nonmalignant cells to the drug. The drug is limited to the extracellular space, and this prevents undesirable effects

of unmodified tetrac inside normal cells. Nanotetrac does not inactivate $\alpha v\beta 3$, as antibody to the integrin may, but selectively manipulates the functions of the integrin, so that apoptosis is fostered and antiapoptosis defenses are disordered. Desirable features of Nanotetrac action that were unexpected are enhanced transcription of antiangiogenic *TSP1* and decreased expression of *EGFR*, of matrix metalloproteinases⁴³ that support tumor aggressiveness, and of cyclins and protooncogenes.^{12,45} Finally, the agent has a complex set of antiangiogenic properties. As noted previously, these include decreasing transcription of genes coding for vascular growth factors and blunting the activity of these factors at their specific receptors adjacent to the integrin on the cell surface.^{13,51}

The poly(lactic-co-glycolic acid) nanoparticle to which tetrac is covalently bound in Nanotetrac is capable of adsorbing traditional nonprotein cancer chemotherapeutic agents. The targeting by tetrac of the nanoparticulate to cancer cells permits local delivery of such second agents, an approach that is more desirable than systemic administration of the drugs.

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Disclosure

Authors PJ Davis and SA Mousa hold US patents on nanoparticulate tetrac (Nanotetrac). The authors report no other conflicts of interest in this work.

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