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Authors

Lechner, Melissa
Brent, Gregory

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A New Twist on a Classic: Enhancing Radioiodine Uptake in Advanced Thyroid Cancer

Melissa G. Lechner,
Gregory A. Brent
Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, UCLA David Geffen School of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA

Summary

Advanced differentiated thyroid cancer that is resistant to radioactive iodine therapy may become responsive with a unique treatment combination of chloroquine and vorinostat. This treatment was demonstrated in cellular and animal models of thyroid cancer to inhibit endocytosis of the plasma membrane bound iodine transporter, NIS, and restore iodine uptake.

In this issue of *Clinical Cancer Research*, Read and colleagues report on a novel approach to augment radioactive iodine (RAI) uptake in cellular and animal models of thyroid cancer, using chloroquine, which inhibits endocytosis of the sodium iodide symporter (NIS) and promotes insertion in the plasma membrane (1). Vorinostat, a histone deacetylase (HDAC) inhibitor, was added in mouse models to enhance NIS gene expression (1). A wide range of approaches have been pursued to augment iodine uptake for treatment of thyroid cancer, including directly enhancing gene expression of NIS, chromatin modifiers, and promoting NIS membrane insertion (2).

Iodine (I^-) is essential for the synthesis of thyroid hormone by thyroid follicular cells and is selectively taken up from the bloodstream into thyroid follicular cells via NIS. Iodine is transported across the cell basolateral membrane into the cytosol, coupled with two sodium (Na^+) ions, driven by a high extracellular to intracellular sodium gradient maintained by the Na-K-ATPase (3). Normal thyroid follicular cells can concentrate iodine up to 30-fold. NIS is an integral plasma membrane glycoprotein with the N-terminus extending towards the extracellular milieu and the C terminus towards the cytosol (4). NIS gene expression is enhanced by thyroid stimulating hormone (TSH), along with the transcription factors NKX2-1 and Pax8 (5). TSH additionally promotes NIS plasma membrane insertion, which is essential for effective iodine transport (5).

Expression and membrane localization of NIS plays a key role in the use of RAI for thyroid cancer imaging and the capacity to deliver β-emitting ^{131}I for therapy. RAI was the first “theranostic” agent, one that can be used for both diagnosis and for targeted

Corresponding author: Gregory A. Brent, MD, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of California Los Angeles David Geffen School of Medicine, 10833 Le Conte Ave, CHS 57-145, Los Angeles, California 90095 USA, gbrent@mednet.ucla.edu.

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therapy, and was shown to effectively treat thyroid cancer over 80 years ago (6). The vast majority of thyroid cancers derive from thyroid follicular epithelial cells, and thus retain some features of normal thyroid cells, albeit at reduced levels, including growth in response to TSH, production of thyroglobulin, and uptake of iodine (7). Standard therapy for differentiated thyroid cancer includes partial or total thyroid surgical resection (8). In addition, patients at high risk of disease persistence or recurrence are treated with an oral dose of RAI for ablation of any remnant normal tissue and destruction of microscopic or macroscopic metastases, often found in the neck or lung (8). Unfortunately, a subset of patients develop RAI refractory differentiated thyroid cancer (RAIR-DTC), including those that never concentrated RAI, lose the ability to concentrate RAI, or have disease progression despite RAI (9). RAI whole body scan imaging is used to monitor thyroid cancer and for treatment, so reduced RAI uptake limits management options.

RAIR-DTC causes the majority of thyroid cancer-related deaths. Effective systemic treatment options remain elusive, despite prior and ongoing trials evaluating multiple kinase inhibitors (MKIs; e.g. lenvatinib and sorafenib), BRAF inhibitors (e.g. dabrafenib, vandetinib) and immune checkpoint inhibitors (e.g. anti-programmed death protein/ligand 1) (10). These therapies provide limited clinical benefit (progression free survival ranging from approximately 4 to 18 months) and carry significant treatment-related side effects that decrease patient quality of life (8). By contrast, RAI therapy promises an effective thyroid tissue-specific systemic therapy with few side effects.

The basis of RAI resistance is reduced uptake and concentration of iodine into thyroid cancer cells (11). An initial focus to restore RAI uptake in thyroid cancers was on agents that augmented NIS gene expression, including signal transduction pathways stimulated by TSH, altering chromatin to promote overall gene expression, and a range or other hormones and agents (11). Interestingly, histological assessment of many radioiodine-resistant thyroid cancers showed a normal, or near normal, expression of NIS mRNA and even NIS protein, but reduced NIS functional membrane insertion (12). Based upon these findings, subsequent studies have focused on the dynamics of NIS membrane insertion as a strategy to increase iodine uptake. Specific residues in NIS responsible for membrane insertion have been identified by the study of inherited mutations associated with congenital hypothyroidism(13).

Read, McCabe, and colleagues previously reported an interaction of NIS with PTTG1 Binding Factor (PBF), a NIS binding factor that is overexpressed in cancer, reduces NIS plasma membrane insertion and therefore reduces radioiodine uptake (14). Building upon this foundation, they now identify the heterotrimeric AP2 adaptor complex (comprised of α1, μ2, and σ2 subunits) as a binding partner of NIS that mediates its endocytosis via clathrin-coated vesicles and recycling away from the cell surface, thus reducing NIS membrane insertion and iodine uptake. AP2 has been shown to play a critical role in basolateral sorting of NIS (15) and modulates the interaction between NIS and PBF. Through a series of *in vitro* experiments, using human cell lines and primary thyrocytes with programmed NIS expression, the authors showed that genetic deletion of AP2 α1 and μ2 subunits or AP2-associated kinase 1 (AAK1), using siRNA, decreased endocytosis of NIS by disrupting the interaction with PBF and significantly enhanced RAI uptake

in NIS-expressing thyroid cancer cell lines. Furthermore, the study identified a specific acidic dileucine motif in the C-terminal region of NIS required for interaction with the σ2 subunit of AP2. Ablation of this key binding motif, or treatment with chloroquine to inhibit the interaction, prevented efficient co-localization of NIS with the AP2 complex for endocytosis and led to increased radioiodine uptake. Thyroid cancer models in mice treated with chloroquine and vorinostat restored NIS transport function. Overexpression of these AP2 complex genes was also correlated with recurrence and RAI resistance in human thyroid cancer genomic databases. Taken together, these data elucidate important mechanisms controlling NIS cell surface retention and potential therapeutic targets for augmenting RAI uptake (Figure 1).

Although a wide range of approaches to enhance NIS gene expression and NIS membrane insertion in pre-clinical models have been effective, the ability to translate these agents to humans has been limited by a number of factors, including the potential toxicity. “Re-differentiation” therapy, using selected kinase inhibitors targeting growth pathways has been shown to improve NIS expression and restore RAI responsiveness in RAIR-DTC. In a clinical study, the mitogen-activated protein kinase (MAPK) pathway inhibitor selumetinib, enhanced RAI uptake in a significant fraction of RAIR-DTC patients (16). A strength of the approach by Read *et al.* is targeting NIS endocytosis using existing FDA-approved therapies, chloroquine and vorinostat, that have a rapid effect on enhancing NIS membrane insertion (1). It is expected that short term treatment with these agents, over a few days, similar to current TSH stimulation in RAI-responsive patient, could augment RAI uptake in RAIR-DTC patients. Future studies to evaluate whether chloroquine and vorinostat can stimulate native NIS in thyroid cancer models and whether this translates to increased thyroid cancer cell death *in vivo* would further support the clinical use of this approach.

Augmentation of NIS membrane insertion and the resulting enhanced radioiodine uptake may be useful in other cancers that express NIS and weakly concentrate iodine, including breast cancer(17), as well as augmenting the effectiveness of NIS gene therapy used for a range of cancers (18). Clinical application in RAIR-DTC will likely rely on a combination of agents, guided by the genetic profile of the tumor, such that chloroquine therapy could be combined with strategies that enhance native NIS expression, including TSH stimulation, HDAC inhibition (e.g. vorinostat), or MAPK inhibition (e.g. selumetinib). Given the significant mortality and limited treatment options for patients with RAIR-DTC, this report by Read *et al.* (1) provides an exciting potential new avenue to improve RAIT responses in thyroid cancer.

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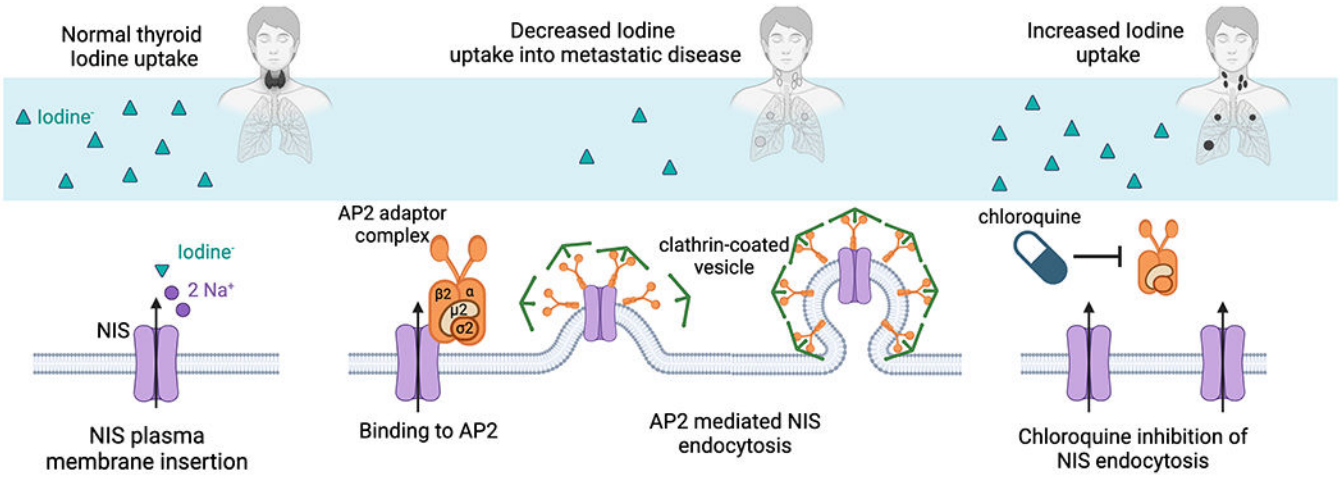

Figure.

Iodine transport in the thyroid is mediated by the integral membrane glycoprotein, sodium iodide symporter (NIS), which transports iodine, coupled with two Na^+, down the sodium gradient, high extracellular to low intracellular. The normal thyroid gland can be imaged by oral administration of radioactive iodine (RAI). The heterotrimeric AP2 adaptor complex (comprised of α1, μ2, and σ2 subunits) is a binding partner of NIS that mediates its endocytosis via clathrin-coated vesicles. AP2 is overexpressed in RAI-resistant differentiated thyroid cancer, RAIR-DTC, and is associated with reduced iodine uptake into metastatic disease. Chloroquine disrupts the interaction of AP2 and NIS, reduces NIS endocytosis and permits greater concentration of radioiodine in thyroid cancer metastases. (Figure created with BioRender.com.)