The Year in Basic Thyroidology

Sheue-Yann Cheng

Basic research in 2019 yielded exciting discoveries and advancements in thyroidology. Specifically, there have been breakthroughs in our understanding of the molecular actions of thyroid hormone and thyroid hormone receptors, thyroid hormone metabolism and transport, autoimmunity, and thyroid cancer. Next, I summarize important studies published over the past year and whose major data I presented during the 89th American Thyroid Association annual meeting at the opening plenary session *The Year in Thyroidology*.

Keywords: thyroid hormone, thyroid hormone receptors, thyroid hormone metabolism and transport, autoimmunity, thyroid cancer

Molecular Actions of Thyroid Hormone and Thyroid Hormone Receptors

Thyroid hormone signaling in human retinal organoids

IN HUMANS, TWO thyroid hormone receptor genes (*THRA* and *THRB*) encode three major thyroid hormone-binding thyroid hormone receptor (TR) isoforms (TR β 1, TR β 2, and TR α 1). The major tissue-specific functions of TR β are the regulation of the pituitary-thyroid axis, liver metabolism, and visual and auditory sensory activities. The major tissue-specific functions of TR α 1 are the regulation of thermogenesis, heart activity, development of the intestine and bone, and neurogenesis and brain functions.

To understand the developmental regulation of cone photoreceptors in human retina, Eldred and colleagues generated human retinal organoids from stem cells (1). Three subtypes of human photoreceptor cones are defined by the visual pigments they express: blue-opsin (short wavelength, S), green-opsin (medium wavelength, M), and red-opsin (long wavelength, L). During the development of human fetal retina, S cones are generated first; L/M cones are specified later. The mechanism that controls the switch from S cones to L/M cones was unknown.

In their study, Eldred and colleagues studied the mechanism that controls the decision between the fate of S and L/M cones in human retinal organoids (1). They first validated that these human organoids have similar distributions, gene expression profiles, and morphologies of cone subtypes as in human retina. Moreover, the temporal switch of S cones to L/M cones in the human retinal organoid was similar to that of the human retina. In organoids in which the *THRB* function was completely ablated (i.e., both TR β 1 and TR β 2) by CRISPR/Cas9 editing, only blue S cones were detected. After treatment of wild-type organoids with the thyroid hormone

(T3), only green L/M clones were found. In contrast, treatment of *THRB*-function-deficient human organoids with T3 could not switch blue S cones to the green L/M cones. These results indicated that thyroid hormone signaling was necessary and sufficient for temporal switch between S and L/M fate specifications.

Next, they asked how T3 concentrations in the retina were regulated to control temporal switch between S and L/M fate specifications and found that the T3 concentrations were regulated by the temporal expression of *DIO2* and *DIO3* in the retina. In the early stage of human retina development, *DIO3* was highly expressed to inactive thyroid hormones. The low thyroid hormone in the retina dictated the expression of S cones. In the later development, *DIO2* was highly expressed to convert T4 to T3 to repress S clones and to induce L/M cones via TR β . The importance of this work lies in its establishing stem cell-derived organoids as a model for determining the mechanism of human development with promising utility for therapy and vision repair.

Novel thyroid hormone actions on thermogenesis and heart regeneration

Hirose and colleagues found evidence for thyroid hormonal control of heart regenerative capacity during endothermy acquisition (2). The investigators asked why the adult mammalian heart loses regenerative capacity and discovered thyroid hormones as a surprising molecular link connecting the loss of mammalian cardiac regenerative potential to the acquisition of postnatal endothermy. They found that loss of heart regenerative capacity in adult mammals is triggered by increasing thyroid hormones: postnatal rise (>50-fold) of thyroid hormones coincided with cardiomyocyte cell-cycle exit and loss of regenerative capacity. However, in the adult

heart with TR α 1 deficiency, cardiomyocyte regenerative capacity was preserved. Further, high total serum T4 and high metabolism or body temperature was associated with low diploid cardiomyocytes and more loss in heart regenerative potential in the mammalian adult heart. In contrast, in the heart of neonatal mice and zebrafish, high content of diploid cardiomyocytes and low body temperature were associated with high regenerative potential. Experimental manipulation of serum thyroid hormone levels in mice and zebrafish led to an increase and a decrease of diploid cardiomyocyte content, respectively.

These findings were further supported by a cardiomyocyte ploidy analysis across 41 vertebrate species by this group (2). The investigators uncovered that certain monotreme, edentate, cetacean, and chiropteran species have unusually high percentages of diploid cardiomyocytes in the adult heart. Further, diploid cardiomyocyte abundance conforms to Kleiber's law—the 3/4-power law scaling of metabolism with bodyweight—and inversely correlates with standard metabolic rate, body temperature, and serum T4 level.

In view of others' findings that cardiomyocyte polyploidization is a major barrier for heart regeneration (3,4), these results suggest that the evolutionary increase of polyploid cardiomyocyte frequency and decline of cardiac regenerative potential may occur in parallel with the ectotherm-to-endotherm transition. As the major driver of energy metabolism and thermogenesis, thyroid hormones seem to be the key factors promoting both heart regenerative potential loss and the acquisition of endothermy.

Why is increased metabolism and thermogenesis positively selected for during mammalian evolution? Elevated metabolic rate and the evolution of endothermy likely offered early mammals survival advantages as they inhabited a temporally wide nocturnal niche and expanded into regions of colder climates previously unexplored by reptiles. The loss of proliferation-competent cells and the decline of regenerative capacity in the heart and other organs were seemingly not under selection pressure in animal evolution. Thus, these findings suggest that the loss of heart regenerative capacity in adult mammals is triggered by increasing thyroid hormones and may be a tradeoff for the acquisition of endothermy.

Thyroid hormone action on myelin repair

It is known that T3 action produces oligodendrocytes, the cells in the central nervous system (CNS) that make myelin. Currently, however, there is no approved myelin repair therapy for multiple sclerosis or other demyelinating diseases. Hartley and associates employed two enabling recent advances to address the question of whether thyroid hormone action in the CNS can have a pro-remyelination effect in a demyelinating *in vivo* model (5). The first advance is the thyromimetic prodrug Sob-AM2 that delivers substantially more of the thyromimetic sobetirome to the CNS from a systemic dose than an equivalent dose of the parent drug sobetirome. The second advance is a newly developed genetic mouse model of demyelination (iCKO-*Myrf* mice). This iCKO-*Myrf* mutant mouse features an inducible knockout of the myelin regulatory factor gene (*Myrf*), essential for mature oligodendrocyte survival. In this model, *Myrf* ablation can be induced by short-term treatment with tamoxifen, and *Myrf* knockout occurs only in mature oligodendrocytes, resulting in CNS-wide demyelination. Induced demyelination in iCKO-*Myrf* mice is

accompanied by a robust and quantifiable motor disability that improves in response to remyelination.

Hartley *et al.* tested sobetirome and Sob-AM2 for therapeutic benefit in motor disability, and they found accelerated CNS remyelination via histology, magnetization transfer imaging, and electron microscopy to evaluate brain and spinal cord myelin status in iCKO-*Myrf* mice. They found that the CNS-penetrating thyromimetics provide significant improvement to motor disability and accelerate remyelination in both brain and spinal cord. Hartley *et al.* also showed that thyromimetic treatment generates a larger population of oligodendrocytes in demyelinated brain regions, thus providing support for the expected mechanism that thyromimetics promote remyelination by stimulated oligodendrogenesis. This study provides preclinical rationale and support for developing CNS-penetrating thyromimetics for the treatment of multiple sclerosis and other demyelinating disease.

Thyroid Hormone Transport and Metabolism

Brain hypothyroidism and deiodinase

In the rat brain, most T3 is generated locally via deiodination of T4, a reaction catalyzed by the type-two deiodinase (D2) (6). The important role that D2 played in generating local T3 in the brain became evident in studies of mice with astrocyte-specific D2 inactivation (7). Despite having normal serum T3 levels, these animals exhibited anxiety-depression-like behavior and a hippocampal transcriptome typical of reduced thyroid hormone signaling (7). No D2 mutations have been reported in humans, but a single nucleotide polymorphism (SNP) from Thr92Ala-D2 is present in 12–36% of the population (8). This SNP does not seem to be associated with cognition or quality of life in euthyroid individuals (9). However, hypothyroid patients who are carriers of the Ala92-D2 SNP exhibited improved quality of life when T3 was added to T4 therapy (10). Even though some of these findings have not been reproduced in another study (9), at face value they suggest that Ala92-D2 carriers on T4 therapy may not produce sufficient amounts of T3 via D2.

Thus, to gain insight into these mechanisms, Jo and colleagues first studied cell lines stably expressing Thr92-D2 or Ala92-D2 tagged with fluorescence probes and found that Ala92-D2 causes endoplasmic reticulum (ER) stress and accumulates in the Golgi apparatus (11). In this setting, Ala92-D2 was found to produce ~20% less T3 in the presence of different T4 concentrations. To further their understanding of Ala92-D2 actions, these investigators used CRISPR genome editing and created mouse strains carrying the Thr92-D2 or the Ala92-D2 gene. The Ala92-D2 mice were systemically euthyroid, growing and reproducing normally. However, they were sensitive to an anxiogenic environment and exhibited higher exploratory activity and more risk-assessment behavior. However, once settled in their home-cage, Ala92-D2 mice refrained from physical activity and exhibited sleepiness and impaired memory. Similarly, the brain of the Ala92-D2 mice exhibited generalized signs of ER stress and diminished thyroid hormone signaling in distinct areas, that is, the striatum, amygdala, and frontal cortex. Enhancing T3 signaling in the brain with the administration of T3 improved cognition. Further, restoring proteostasis with the chemical chaperone 4-phenyl butyric acid treatment eliminated the Ala92-D2 phenotype. In contrast, primary

hypothyroidism intensified the Ala92-D2 phenotype, with only partial response to T4 therapy.

Based on these findings, the authors concluded that disruption of cellular proteostasis and reduced Ala92-D2 activity may contribute to the failure of T4 therapy in carriers of Ala92-D2 SNP. Although presently there is no evidence that carriers of the Ala92-D2 polymorphism exhibit brain hypothyroidism, the study of the cerebral cortex of Ala92-D2 carriers revealed a transcriptional fingerprint, suggestive of neurodegenerative diseases, with activation of the ubiquitin pathway, mitochondrial dysfunction, inflammation, apoptosis, DNA repair, and growth factor signaling (12). Moreover, in African Americans, Ala92-D2 was associated with molecular markers known to underlie Alzheimer's disease, and with increased odds of developing Alzheimer's disease/dementia (13). The authors conclude that these findings need to be reproduced by other groups before Ala92-D2 SNP could be used to guide treatment of hypothyroid patients.

Defective organic anion transporting polypeptide 1C1 transporter in a patient with impaired brain functions

T4 transport across the blood–brain barrier is predominately mediated by monocarboxylate transport 8 (MCT8), while T4 uptake by astrocytes is facilitated by organic anion transporting polypeptide 1C1 (OATP1C1). MCT8 patients with Allan-Herndon-Dudley syndrome have been described; however, until now, patients with *OATP1C1* defects have not been reported. While *OATP1C1* knockout mice develop normally without any overt neurological abnormality, the knockout mice have nervous system-specific hypothyroidism.

Stromme and associates reported the first case—a 15.5-year-old girl who had a mutation in *OATP1C1* that was associated with severe brain hypometabolism and juvenile neurodegeneration (14). The girl was developed normally in her first year of life, but she gradually exhibited dementia with spasticity and intolerance to cold. Brain imaging showed gray and white matter degeneration and severe glucose hypometabolism. Whole-exome sequencing of the 15.5-year-old girl identified a homozygous missense mutation in *OATP1C1* in a highly conserved site with an aspartic acid 252 to asparagine (D252N) amino acid change. Functional characterization showed that T4 uptake capacity was reduced in the mutant as well as in the cell surface expression of mutated OATP1C1.

Based on these findings, the investigators treated the patient with Triac co-administered with a low dose of T4. The patient's condition improved after 6 weeks, with the patient resuming eye contact and becoming more alert, being able to swallow better, and having improvements in motor function and her cold intolerance. The identification of the first patient supported the link between defective OATP1C1 functions and neurodegeneration. Future studies in the identification of additional patients with *OATP1C1* mutations will help advance an understanding of the mechanisms underlying the disease-related impaired T4 transport to the brain.

Autoimmunity

Thyrocyte death and autoimmunity

Autoimmune hyperthyroidism, commonly referred to as Graves' disease (GD), is caused by stimulating autoantibodies

to the thyrotropin (TSH) receptor (TSHR). TSHR is a heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptor (GPCR). Previous studies showed that in contrast to stimulating TSHR autoantibodies, antibodies that recognize the linear epitopes in the cleavage region of the TSHR ectodomain (C-TSHR-Abs) induce apoptosis of thyrocytes.

Morshed and colleagues investigated how and why C-TSHR-Abs are capable of initiating a cascade of signaling events that lead to programmed thyrocyte cell death (15). Extensive analyses using live-cell imaging of intracellular vesicular trafficking, endocytosis, proteomic arrays, and fluorescence quantification led to the findings that S-TSHR-mAb activates major G proteins and behaves similarly to TSH (15). However, C-TSHR-mAb failed to activate G proteins and did not undergo normal endosomal and lysosomal vesicular trafficking. Moreover, the accumulated C-TSHR-mAbs induced cellular stress, caused TSHR-biased danger signaling, generated ROS, and activated apoptosis, leading to exacerbation of thyroid autoimmunity. These findings suggest that G proteins in thyrocytes are required not only for GPCR signaling but also for vesicular trafficking and sorting, a process that is independent of cAMP, PKA, and CREB. Further, C-TSHR-Abs may orchestrate overt intrathyroidal, intraorbital, or epidermal inflammatory autoimmune reactions in GD.

Thyroid Cancer

Non-pumping pro-tumorigenic actions of the sodium iodide symporter

The sodium iodide symporter (NIS) is classically localized within the plasma membrane of thyrocytes and thyroid cancer cells, where it mediates iodide uptake and forms the basis of radioiodine therapy for thyroid disease (16–18). Radioiodide uptake is generally lower in thyroid cancer cells than normal thyroid tissue (19). Intriguingly, intracellular non-membranous NIS expression has been reported to be elevated in thyroid and other nonthyroidal cancers (20). This observation led investigators in the Charis Eng laboratory to ask whether NIS can have a pump-independent function. Because thyroid cancer is one of the major components of Cowden's syndrome (21), a subset of which is caused by germline mutations in *PTEN*, the investigators studied the noncanonical tumorigenic role of NIS in thyroid cancer cells in relation to PTEN signaling.

Feng and colleagues reported that cytoplasmic NIS protein interacts with LARG (leukemia-associated RhoA guanine exchange factor) to activate RhoA, thereby enhancing cell migration and invasion in thyroid cancer cells (22). These data supported their working hypothesis that NIS has a pro-tumorigenic function besides its classical iodide pump function in thyroid cancer cells. Importantly, the team found that PTEN siRNA-mediated knockdown results in increased NIS protein levels, especially cytoplasmic NIS, in several thyroid cell lines with exogenous NIS expression, independent of its mRNA expression. Further, they elucidated that PTEN loss activates AKT-mTOR signaling to inhibit NIS glycosylation, subsequently impairing NIS membrane localization. These signaling perturbations resulted in mis-localization of NIS to the cytoplasm, endowing it with the ability to interact with the cytoplasmic protein LARG, which, in turn, increases intracellular NIS stability through these interactions. In addition, their data also indicate that PTEN signaling impacts

the glycosylating enzyme DPAGT1 to then regulate NIS glycosylation. Importantly, they found that PI3K/AKT/mTOR inhibitors not only increase plasma membrane NIS through enhancing NIS glycosylation but also decrease intracellular NIS, indicating these pharmacologic agents' therapeutic role in thyroid cancer, from the standpoint of clearance of the pro-tumorigenic non-pump-function of NIS.

The uncovering of a non-pump function of NIS has added a venue for further exploring the biology of NIS and its actions in thyroid carcinogenesis (23), providing one possible mechanism to explain the more aggressive behavior in cancers with lower radioiodide uptake. Some studies have investigated the potential application of NIS gene therapy in the treatment of iodide refractory thyroid cancers and some nonthyroidal cancers (24). As such, therapeutic strategies should go beyond just increasing NIS protein levels: Effective therapies should promote NIS localization back to the plasma membrane.

Clone originality of anaplastic thyroid cancer

Anaplastic (undifferentiated) thyroid cancer (ATC) is commonly found to co-exist with differentiated thyroid cancers (DTC) such as papillary and follicular thyroid cancer, suggesting that ATC could develop from DTC. However, whether ATC evolves from DTC has been a long-standing issue of debate. Dong and colleagues performed whole-exome sequencing of five ATC tumors with co-existing DTC and matched normal tissue to determine whether there is a shared common ancestor (25). Phylogenetic analysis revealed that in every ATC-DTC pair, a significant number of somatic mutations and somatic copy-number variations were shared, including multiple known cancer drivers. Clonal analysis further demonstrated that each ATC-DTC pair shared a common ancestor, with some pairs diverging early in their evolution and others in which the ATC seems to arise directly from a sub-clone of DTC. Although the precise lineal relationship requires further clarification, based on the genetic relationship, this study suggests a shared origin of ATC and DTC. These findings also raised the consideration as to whether a more aggressive treatment of DTC would be justified to prevent DTC from transitioning into deadly ATC.

Targeting c-MYC in ATC

c-MYC is a critical oncogene, frequently over-expressed in human ATC. c-MYC is one of the most sought-after drug targets for cancer therapy. However, targeting c-MYC has presented a huge challenge as c-MYC lacks binding pockets on its surface owing to its disordered protein structure. A strategy that has been used to target c-MYC is the use of small-molecule inhibitors (e.g., JQ1) to disrupt the interaction of the bromodomain and extraterminal domain (BET) family of proteins with acetylated histones on the chromatin (26).

Zhu and colleagues investigated the effect of targeting c-MYC transcription program via suppression of its super-enhancers on chromatin by using an inhibitor of the activity of BET proteins, for example, BRD4, PLX51107 (PLX). They further tested the efficacy of combined treatment on human ATC cell-derived xenograft tumors with an MEK inhibitor, PD0325901 (PD) (27). They found that the BET inhibitor PLX or the MEK inhibitor PD as a single treatment effectively suppressed the growth of xenograft tumors.

However, the combination treatment was far more effective. Mechanistically, PLX and PD converge to potentially inhibit the binding of BRD4 to the c-MYC promoter to suppress c-MYC transcription, and PD further suppresses MEK signaling to inhibit tumor growth. Recent studies have uncovered mutations of genes involved in chromatin modifiers and transcription regulators in ATC (28). Thus, targeting transcription programs that are critical for cancer progression as shown in the present studies is an effective strategy for novel treatment approaches for ATC.

Acknowledgments

The author thanks Drs. Guo Huang, Tom Scanlan, Antonio Bianco, Charis Eng, and Electron Kebebew for valuable discussions and contributions. The author sincerely apologizes to the colleagues whose work could not be included because of time constraints and length limitations.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

References

1. Eldred KC, Hadyniak SE, Hussey KA, Brennerman B, Zhang PW, Chamling X, Sluch VM, Welsbie DS, Hattar S, Taylor J, Wahlin K, Zack DJ, Johnston RJ Jr. 2018 Thyroid hormone signaling specifies cone subtypes in human retinal organoids. *Science* **362**:eaau6348.
2. Hirose K, Payumo AY, Cutie S, Hoang A, Zhang H, Guyot R, Lunn D, Bigley RB, Yu H, Wang J, Smith M, Gillett E, Muroy SE, Schmid T, Wilson E, Field KA, Reeder DM, Maden M, Yartsev MM, Wolfgang MJ, Grützner F, Scanlan TS, Szweda LI, Buffenstein R, Hu G, Flamant F, Olgin JE, Huang GN 2019 Evidence for hormonal control of heart regenerative capacity during endothermy acquisition. *Science* **364**:184–188.
3. Gonzalez-Rosa JM, Sharpe M, Field D, Soonpaa MH, Field LJ, Burns CE, Burns CG 2018 Myocardial polyploidization creates a barrier to heart regeneration in zebrafish. *Dev Cell* **44**:433–446. e437.
4. Patterson M, Barske L, Van Handel B, Rau CD, Gan P, Sharma A, Parikh S, Denholtz M, Huang Y, Yamaguchi Y, Shen H, Allayee H, Crump JG, Force TL, Lien CL, Makita T, Lusa AJ, Kumar SR, Sucov HM 2017 Frequency of mononuclear diploid cardiomyocytes underlies natural variation in heart regeneration. *Nat Genet* **49**:1346–1353.
5. Hartley MD, Banerji T, Tagge IJ, Kirkemo LL, Chaudhary P, Calkins E, Galipeau D, Shokat MD, DeBell MJ, Van Leuven S, Miller H, Marracci G, Pocius E, Banerji T, Ferrara SJ, Meinig JM, Emery B, Bourdette D, Scanlan TS 2019 Myelin repair stimulated by CNS-selective thyroid hormone action. *JCI Insight* **4**:126329.
6. Crantz FR, Silva JE, Larsen PR 1982 An analysis of the sources and quantity of 3,5,3'-triiodothyronine specifically bound to nuclear receptors in rat cerebral cortex and cerebellum. *Endocrinology* **110**:367–375.

7. Bocco BM, Werneck-de-Castro JP, Oliveira KC, Fernandes GW, Fonseca TL, Nascimento BP, McAninch EA, Ricci E, Kvárta-Papp Z, Fekete C, Bernardi MM, Gereben B, Bianco AC, Ribeiro MO 2016 Type 2 deiodinase disruption in astrocytes results in anxiety-depressive-like behavior in male mice. *Endocrinology* **157**:3682–3695.
8. Mentuccia D, Proietti-Pannunzi L, Tanner K, Bacci V, Pollin TI, Poehlman ET, Shuldiner AR, Celi FS 2002 Association between a novel variant of the human type 2 deiodinase gene Thr92Ala and insulin resistance: evidence of interaction with the Trp64Arg variant of the beta-3-adrenergic receptor. *Diabetes* **51**:880–883.
9. Wouters HJ, van Loon HC, van der Klauw MM, Elderson MF, Slagter SN, Kobold AM, Kema IP, Links TP, van Vliet-Ostapchouk JV, Wolffenbuttel BH 2017 No effect of the Thr92Ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. *Thyroid* **27**:147–155.
10. Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM 2009 Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. *J Clin Endocrinol Metab* **94**:1623–1629.
11. Jo S, Fonseca TL, Bocco BMLC, Fernandes GW, McAninch EA, Bolin AP, Da Conceição RR, Werneck-de-Castro JP, Ignacio DL, Egri P, Németh D, Fekete C, Bernardi MM, Leitch VD, Mannan NS, Curry KF, Butterfield NC, Bassett JHD, Williams GR, Gereben B, Ribeiro MO, Bianco AC 2019 Type 2 deiodinase polymorphism causes ER stress and hypothyroidism in the brain. *J Clin Invest* **129**:230–245.
12. McAninch EA, Jo S, Preite NZ, Farkas E, Mohácsik P, Fekete C, Egri P, Gereben B, Li Y, Deng Y, Patti ME, Zevenbergen C, Peeters RP, Mash DC, Bianco AC 2015 Prevalent polymorphism in thyroid hormone-activating enzyme leaves a genetic fingerprint that underlies associated clinical syndromes. *J Clin Endocrinol Metab* **100**:920–933.
13. McAninch EA, Rajan KB, Evans DA, Jo S, Chaker L, Peeters RP, Bennett DA, Mash DC, Bianco AC 2018 A common DIO2 polymorphism and alzheimer disease dementia in African and European Americans. *J Clin Endocrinol Metab* **103**:1818–1826.
14. Stromme P, Groeneweg S, Lima de Souza EC, Zevenbergen C, Torgersbråten A, Holmgren A, Gurcan E, Meima ME, Peeters RP, Visser WE, Høneren Johansson L, Babovic A, Zetterberg H, Heuer H, Frengen E, Misceo D, Visser TJ 2018 Mutated thyroid hormone transporter OATP1C1 associates with severe brain hypometabolism and juvenile neurodegeneration. *Thyroid* **28**:1406–1415.
15. Morshed SA, Ma R, Latif R, Davies TF 2018 Biased signaling by thyroid-stimulating hormone receptor-specific antibodies determines thyrocyte survival in autoimmunity. *Sci Signal* **11**:eaah4120.
16. Dai G, Levy O, Carrasco N 1996 Cloning and characterization of the thyroid iodide transporter. *Nature* **379**:458–460.
17. Smanik PA, Ryu KY, Theil KS, Mazzaferri EL, Jhiang SM 1997 Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. *Endocrinology* **138**:3555–3558.
18. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L 2016 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **26**:1–133.
19. Kogai T, Brent GA 2012 The sodium iodide symporter (NIS): regulation and approaches to targeting for cancer therapeutics. *Pharmacol Ther* **135**:355–370.
20. Wapnir IL, van de Rijn M, Nowels K, Amenta PS, Walton K, Montgomery K, Greco RS, Dohán O, Carrasco N 2003 Immunohistochemical profile of the sodium/iodide symporter in thyroid, breast, and other carcinomas using high density tissue microarrays and conventional sections. *J Clin Endocrinol Metab* **88**:1880–1888.
21. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C 2012 Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res* **18**:400–407.
22. Feng F, Yehia L, Ni Y, Chang YS, Jhiang SM, Eng C 2018 A nonpump function of sodium iodide symporter in thyroid cancer via cross-talk with PTEN signaling. *Cancer Res* **78**:6121–6133.
23. Feng F, Yehia L, Eng C 2019 Pro-tumorigenic non-pump function of sodium iodide symporter: a reimagined Trojan horse? *Oncotarget* **10**:688–689.
24. Spitzweg C, O'Connor MK, Bergert ER, Tindall DJ, Young CY, Morris JC 2000 Treatment of prostate cancer by radioiodine therapy after tissue-specific expression of the sodium iodide symporter. *Cancer Res* **60**:6526–6530.
25. Dong W, Nicolson NG, Choi J, Barbieri AL, Kunstman JW, Abou Azar S, Knight J, Bilguvar K, Mane SM, Lifton RP, Korah R, Carling T 2018 Clonal evolution analysis of paired anaplastic and well-differentiated thyroid carcinomas reveals shared common ancestor. *Genes Chromosomes Cancer* **57**:645–652.
26. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastiris E, Gilpatrick T, Paranal RM, Qi J, Chesi M, Schinzel AC, McKeown MR, Heffernan TP, Vakoc CR, Bergsagel PL, Ghobrial IM, Richardson PG, Young RA, Hahn WC, Anderson KC, Kung AL, Bradner JE, Mitsiades CS 2011 BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell* **146**:904–917.
27. Zhu X, Park S, Lee WK, Cheng SY 2019 Potentiated anti-tumor effects of BETi by MEKi in anaplastic thyroid cancer. *Endocr Relat Cancer* [Epub ahead of print] DOI: 10.1530/ERC-19-0107.
28. Landa I, Ibrahimasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, Schultz N, Berger MF, Sander C, Taylor BS, Ghossein R, Ganly I, Fagin JA 2019 Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J Clin Invest* **126**:1052–1066.

Address correspondence to:
Sheue-Yann Cheng, PhD
Laboratory of Molecular Biology
Center for Cancer Research
National Cancer Institute
National Institutes of Health
37 Convent Drive, Room 5128
Bethesda, MD 20892-4264

E-mail: chengs@mail.nih.gov