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REVIEW ARTICLE

Advances in the molecular mechanism and targeted therapy of radioactive-iodine refractory differentiated thyroid cancer

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Abstract

Most patients with differentiated thyroid cancer have a good prognosis after radioactive iodine-131 treatment, but there are still a small number of patients who are not sensitive to radioiodine treatment and may subsequently show disease progression. Therefore, radioactive-iodine refractory differentiated thyroid cancer treated with radioiodine usually shows reduced radioiodine uptake. Thus, when sodium iodine symporter expression, basolateral membrane localization and recycling degradation are abnormal, radioactive-iodine refractory differentiated thyroid cancer may occur. In recent years, with the deepening of research into the pathogenesis of this disease, an increasing number of molecules have become or are expected to become therapeutic targets. The application of corresponding inhibitors or combined treatment regimens for different molecular targets may be effective for patients with advanced radioactive-iodine refractory differentiated thyroid cancer. Currently, some targeted drugs that can improve the progression-free survival of patients with radioactive-iodine refractory differentiated thyroid cancer, such as sorafenib and lenvatinib, have been approved by the FDA for the treatment of radioactive-iodine refractory differentiated thyroid cancer. However, due to the adverse reactions and drug resistance caused by some targeted drugs, their application is limited. In response to targeted drug resistance and high rates of adverse reactions, research into new treatment combinations is being carried out; in addition to kinase inhibitor therapy, gene therapy and rutin-assisted iodine-131 therapy for radioactive-iodine refractory thyroid cancer have also made some progress. Thus, this article mainly focuses on sodium iodide symporter changes leading to the main molecular mechanisms in radioactive-iodine refractory differentiated thyroid cancer, some targeted drug resistance mechanisms and promising new treatments.

Keywords Autophagy · Radioactive-iodine refractory differentiated thyroid cancer · Molecular mechanisms · Molecular interactions · Targeted therapy

Abbreviations

FDA	Food and drug administration
ATA	American Thyroid Association
RAIR-DTC	Radioactive-iodine refractory differentiated thyroid cancer
RAI	Radioiodine
NIS	Sodium iodine symporter
TERT	Telomerase reverse transcriptase
TGF-β1	Transforming growth factor-β1
SMAD3	Mothers against DPP homolog 3 (Drosophila)
WNT1	Wingless-type MMTV integration site family, member 1
ROS	Reactive oxygen species
FDG	β-2- [18 F]-Fluoro-2-deoxy-D-glucose
SLC5A5	Solute carrier family 5
SCRIB	Scribbled homolog (Drosophila)
AP-1A	Adaptor protein complex-1A
AP-1B	Adaptor protein complex-1B
TGN	Trans-Golgi network
PTTG	Pituitary tumor transforming gene
PBF/PTTG1IP	Pituitary tumor transforming gene binding factor
TCF/LEF	T-cell Factor/Lymphoid Enhancing Factor

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DACT2	Dapper, antagonist of beta-catenin, homolog 2 (Xenopus laevis)
HIF-1α	Hypoxia-inducible factor-1α
KDM1A/LSD1	Histone lysine-specific demethylase1
APC2	Adenomatosis polyposis coli 2
DDK1	Dickkopf-related protein 1
NOX1	NADPH oxidase 1
NRX	Nucleoredoxin
ARF4	ADP-ribosylation factor 4
VCP	Valosin protein
ERAD	Endoplasmic reticulum-associated protein degradation
PM	Plasma membrane
IGF2BP2	Insulin-like growth factor 2 mRNA binding protein 2
RUNX2	Runt-related transcription factor 2
SAHA	N-Hydroxy-N'-phenyloctanediamide
PAX8	Paired box gene 8
NKX2-1	NK2 homeobox 1
TSHR	Thyroid stimulating hormone receptor
TSH	Thyroid stimulating hormone
PIGU	One of the components of the glycosyl phosphatidylinositol aminositol transaminase (GPIT) complex
CREB3L1	CAMP responsive element binding protein 3-like 1
mTORC1/2	Mammalian target of rapamycin compelx1/2
NMTC	Nonmyelinary thyroid cancer
AMPK	Adenosine 5'-monophosphate (AMP)-activated protein kinase
ULK1	Unc-51-like kinase 1 (C. elegans)
TFEB	Transcription factor E3
CARM1	Coactivator-associated arginine methyltransferase 1
SKP2	S-phase kinase-associated protein 2 (p45)
SHP	Small heterodimer partner
FOXO3	Forkhead box O3
WT1	Wilms' tumor 1
FOXP3	Forkhead box P3
NADPH	(Reduced) Nicotinamide adenine dinucleotide phosphate
NOX4	NADPH oxidase 1
DNMT1	Recombinant DNA methyltransferase 1
HDAC	Histone deacetylase
Src	Nonreceptor tyrosine kinase
HMGB1	High mobility group protein B1
ERS	Endoplasmic reticulum stress
UPR	Unfolded protein response
LC3-I	Microtubule-associated protein 1 light chain 3
PERK	PKR-like ER kinase
eIF2α	Eukaryotic initiation factor 2α
ATF4	Recombinant activating transcription factor4
CHOP	C/EBP-homologous protein
ERO1α	ER REDOX hormone 1α
IP3R1	Inositol 1,4,5-triphosphate receptor 1
CaMMII	Calmodulin-dependent protein kinase II
NOX2	NADPH oxidase 2
SIRT6	Sirtuin (silent mating type information regulation 2 homolog) 6 (S. cerevisiae)
NRROS	Negative regulator of reactive oxygen species
TME	Tumor microenvironment
MDSCs	Myeloid-derived suppressor cells
Gpx4	Glutathione peroxidase-4
GSH	Glutathione
SLC3A2	Solute carrier family 3 member 2
SLC7A11	Solute carrier family 7 member 11
PHKG2	Phosphorylase kinase G2
PUFAs	Polyunsaturated fatty acids
ACSL4	Acyl-CoA synthetase long-chain family 4
PTGS2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)
IR	Ionizing radiation
NRF2	NFE2-related factor 2
NFE2L2	Nuclear factor (erythroid-derived 2)-like 2
ESCC	Esophageal squamous cell carcinoma
EZH2	Enhancer of zeste homolog 2
ERBB2	V-erb-b2 erythroblastic leukemia viral oncogene homolog 2
ICB	Immune checkpoint blockade
CTLA4	Cytotoxic T-lymphocyte antigen 4
PD1	Programmed cell death protein 1
PDL1/2	Programmed cell death-ligand 1/2
TBX3	T-box transcription factor 3
CXCR2	CXC-chemokine receptor 2
PMN-MDSCs	Polymorphonuclear myeloid suppressor cells
RGI	Reporter gene imaging
AIDS	Acquired/immunodeficiency/syndrome
cAMP	Cyclic adenosine monophosphate
CREB	CAMP-response element binding protein
VnNp	Vanadium pentoxide nanoparticles

Introduction

In 2020, 586,202 cases of thyroid cancer (TC) were reported worldwide, and TC ranked tenth among the most common carcinomas globally [1]. The pathological types of TC include papillary thyroid cancer (PTC, 80–85%); follicular thyroid cancer (FTC, 10–15%); Hurthle cell cancer of the thyroid gland, a special type of FTC; anaplastic thyroid cancer (ATC); and medullary thyroid cancer (MTC). Because of the better prognosis of the first and second pathological types, they are called differentiated thyroid cancer (DTC), accounting for more than 90% of the total TC cases diagnosed each year. Most patients with DTC have a good prognosis after surgical thyroidectomy, selective radioiodine (RAI) therapy, selective lymph node dissection (in the case of PTC and FTC), and thyroid hormone replacement therapy, with a 10-year overall survival rate of 85%. However, although the mortality rate of DTC patients is low, a small proportion (15%) of DTC patients still have a high risk of disease progression; for example, the risk of local recurrence and distant invasion and metastasis are 20% and 10%, respectively, which leads to poor prognosis of such patients, and the 10-year overall survival rate is less than 10% [2, 3].

In recent years, studies on the pathogenesis of RAIR-DTC have been carried out continuously. With the deepening of research, an increasing number of molecules that may be involved in the pathogenesis of RAIR-DTC in different ways have been identified. Sodium iodine symporter (NIS) plays a key role in the normal uptake of iodine from blood by cells. For DTC cells, the abnormal expression of NIS, transport, recycling and degradation may make them insensitive to RAI treatment [4, 5].

Many studies have demonstrated the effects of BRAF V600E mutation, TERT gene mutation, the TGF-β1/SMAD3 pathway and the WNT1/β-catenin pathway on NIS [6–11]. For most solid tumors, hypoxia and nutrient deficiency are challenges during growth. Tumor cells can protect themselves through various mechanisms so they can tolerate the adverse growth environment. For example, in established cancers, autophagy can help cancer cells address environmental stress, such as hypoxia, nutrient deficiency or cancer treatments [12, 13]. Studies have confirmed that activation of the autophagy pathway can promote NIS degradation by autophagic lysosomes, which increase NIS degradation and may lead to the occurrence of RAIR-DTC [14]. In addition, the redox status of cells can affect NIS expression in different ways [15], and autophagy and reactive oxygen species (ROS) have complex interactions, which were reviewed in detail by Hasan et al. [16]. Autophagy and ROS may affect NIS content alone or together, ultimately resulting in insensitivity to RAI treatment. In addition, some classical pathways, such as the TGF-β1/SMAD3 pathway and WNT1/β-catenin, also interact with autophagy and ROS. Therefore, further study of the interactions between various factors affecting NIS molecules in DTC cells may be important to improve the understanding of the molecular mechanism of RAIR-DTC. Moreover, studies on RAIR-DTC targeted therapy have been carried out continuously, and the kinase inhibitors sorafenib and lenvatinib were shown to have no effect on the overall survival of patients but could improve the progression-free survival of patients. However, due to the development of drug resistance, other kinase inhibitors or combination therapies, such as MAPK/MEK inhibitors combined with RAIR-DTC for BRAF V600E mutation, are also being studied. The combination of the HER inhibitor lapatinib and a BRAF/MEK inhibitor in the treatment of PTC caused by the BRAFV600E mutation is more effective than the inhibitor alone.

In summary, this paper mainly focuses on the pathogenesis of RAIR-DTC, further discusses the possible reticular regulatory effect among factors affecting NIS, and discusses the future application potential of late RAIR-DTC targeted therapy based on kinase inhibitors.

Definition of RAIR-DTC

After surgical treatment, DTC patients usually need to undergo RAI to ablate the residual TC cells or adjuvant therapy. Most patients are sensitive to RAI treatment, but a small number of patients still have poor sensitivity to RAI treatment, that is, iodine refractoriness [4, 17]. With regard to RAIR-DTC, the 2015 ATA guidelines were defined using the following criteria: (1) Patients with malignant/metastatic disease cannot concentrate RAI at the time of initial treatment; (2) Prior treatment showed evidence of sensitivity to RAI therapy, but subsequently the patient's tumor lost its ability to concentrate RAI; (3) Only the local lesion of the patient has the ability to concentrate RAI; (4) The lesion has the ability to concentrate RAI, but some patients still develop disease progression and metastatic disease after high-dose treatment. Although the definition of RAIR-DTC is still slightly controversial due to the different administration times of RAI, cumulative dose and FDG intake in the lesion during the actual treatment, the definition can be further refined through clinical experience in the future, thereby reducing this controversy [6, 18].

Relationship between NIS and RAIR-DTC

NIS is a transmembrane protein located in the basolateral membrane of the thyroid gland, is encoded by the SLC5A5 gene, and plays a key role in transporting I- from the blood to thyroid follicular epithelial cells [5]. Therefore, abnormal NIS plays a key role in the production of RAIR-DTC; that is, any cause of abnormal expression, transport or degradation of NIS will make DTC patients insensitive to RAI treatment [4]. Next, the causes of NIS changes will be discussed in detail.

Abnormal targeted transport and degradation of NIS to the basolateral membrane

NIS is normally localized in the basolateral membrane of follicular epithelial cells for normal uptake of iodine. However, in TC cells, if plasma membrane (PM) transport is defective, NIS expression will often appear in the intracellular compartment. The iodine sensitivity of DTC patients depends on functional NIS expression. Therefore, clarifying the mechanism of NIS PM-targeted trafficking abnormalities can provide new therapeutic targets and ideas for RAIR-DTC.

Influence of PM itself on NIS

It has been found that PM localization and function of NIS depend on its binding to SRC kinase, and that post-PM interaction adherent-binding (AJ) associated P120-catenin is recruited and phosphorylated by SRC, enabling it to recruit RAC1 into the complex. Small GTPase RAC1 is recruited and activated by VAV2 exchange factor phosphorylated by SRC. RAC1 then promotes ARP2/3 mediated actin polymerization via its downstream molecules PAK1 and PIP5K. And the recruitment and binding of the actin anchor protein EZRIN to NIS, promoting its residence and function in normal cells and TC cell PM [19, 20]. Therefore, RAIR-DTC due to the above reasons may require the use of drugs that improve cell–cell adhesion and NIS PM retention in RAIR-DTC cells.

PDZ-binding motifs and NIS targeted basolateral membrane transport and localization

PDZ is a protein containing at least one PDZ domain that determines the transport and localization of transmembrane proteins in specific membrane domains or intracellular compartments. The PDZ binding motif is a PM retention signal. SCRIB, a protein containing the PDZ domain, stabilizes NIS expression at the basolateral PM and prevents NIS from entering lysosomes for degradation. When the PDZ binding motif of the NIS carboxyl terminus is absent, NIS will enter the late endosome-lysosomal pathway for degradation. Notably, PDZ-binding motifs are critical for the correct expression of NIS in the basolateral membrane but are not involved in NIS sorting to the basolateral membrane [21].

Clathrin adaptor proteins and NIS targeted-basolateral membrane transport

Basal sorting signals are simple peptide motifs in proteins, including tyrosine, single leucine, double leucine residues and PDZ binding motifs [22]. A highly conserved single leucine-based ordering motif in the NIS carboxyl terminus that determines the basolateral expression of NIS was identified. Computer simulation showed that the AP-1B-σ1 subunit can recognize the single leucine-based ordering motif in the NIS carboxyl terminus. Unfortunately, studies have not provided biochemical data on the interaction between NIS and AP-1B [23]. Another study demonstrated that the clathrin-associated adaptor AP-1 complex mediates NIS basolateral PM sorting and that adaptor AP-1A binds to residues L121 and LL562/563 on NIS and AP-1B binds to residues L583 on NIS. After total glycosylation of NIS at the Golgi, AP-1 binds to NIS at the TGN, and AP-1A-rich vesicles mediate direct NIS transport from the TGN to the basolateral side via clathrin-coated vesicles. Ap-1b-rich vesicles translocated to circulating endosomes are involved in the recognition of single nucleotide motifs and NIS sequencing from circulating endosomes to the basolateral PM. Therefore, the loss of any of the above molecules will reduce the transport of NIS to the PM. In nonpolarized cells of RAIR-DTC, the basolateral sorting of NIS is abnormal, and a decreased content of AP-1A can be found, which may be one of the factors leading to the insensitivity of DTC to iodine therapy [21, 22] (Fig. 1). In addition, pituitary tumor transforming gene (PTTG) binding factor (PBF/PTTG1IP) can colocalize with NIS and alter the subcellular localization of NIS [24]. The phosphorylation of the Y174 residue by SRC is essential for the interaction between PBF and NIS, and the phosphorylation of the PBF tyrosine residue (Y174) can affect its interaction with the clathrin-associated adaptor complex and affect the colocalization of PBF and NIS [25].

β-catenin promotes NIS degradation

The WNT/β-catenin classical pathway can regulate cell growth, proliferation, etc. This pathway is mainly composed of WNT, WNT ligand and β-catenin. The WNT protein is a highly conserved cysteine-rich glycoprotein family. When WNT binds to the Frizzled receptor and LRP5/6, β-catenin is activated and then enters the nucleus to exert its effect

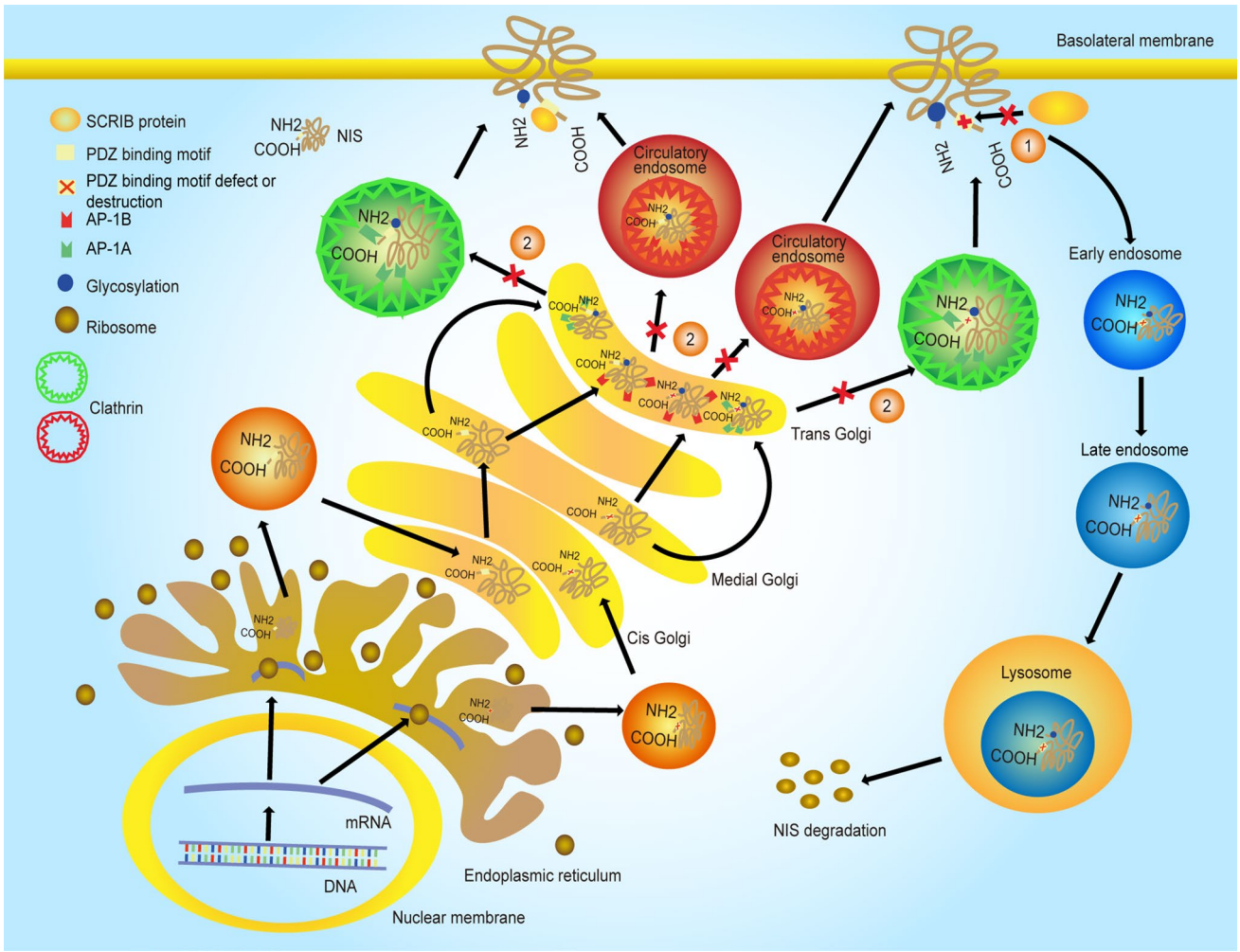

Fig. 1 Diagram of the NIS transport mode. (1) PDZ-binding motifs are associated with the normal expression of the NIS basolateral membrane. The loss of PDZ-binding motifs does not affect NIS basolateral membrane sorting, but the loss of PDZ-binding motifs will reduce the expression of NIS in the basolateral membrane and eventually result in lysosomal degradation. (2) The clathrin adaptor proteins AP-1A and AP-1B are involved in the sorting of NIS to the basolateral membrane, and the reduction in AP-1A/AP-1B expression will affect the sorting of NIS to the basolateral membrane and cause it to remain in the cell

[6, 26]. Activation of this pathway plays a double-edged role in thyroid growth under physiological conditions because β-catenin can interact with Pax8 to increase the transcriptional activity of the NIS gene, which is critical for thyroid physiology. However, this pathway can also promote tumorigenesis. If β-catenin enters the nucleus and is combined with TCF/LEF, cyclin D1 and other downstream molecules can be activated and finally promote tumor cell carcinogenesis and metastasis. DACT2 can inhibit the proliferation and metastasis of thyroid cancer cells by inhibiting the WNT/β-catenin signaling pathway [27, 28].

Hypoxia-inducible factor-1α (HIF-1α) is highly expressed in TC cell lines [29]. β-catenin activity may affect the efficacy of RAI in the treatment of invasive TC cells and is related to the localization of NIS. The HIF-1α/β-catenin/NIS signaling axis was established for the first time. When the expression of HIF-1α increased, the expression of β-catenin also increased, and NIS was transferred from the cell membrane to the cytoplasm, which reduced the uptake of RAI by cells. Once the expression of β-catenin is inhibited, the aggressive FTC cells caused by overexpression of HIF-1α can be completely inhibited by RAI treatment, but the detailed regulatory effect of β-catenin on NIS was not explored in this study [9]. KDM1A/LSD1 (histone lysine-specific demethylase) was found to be overexpressed in PTC tissues and cell lines [30]. KDM1A/LSD1 can directly regulate the demethylation of H3KME1/2 on APC2 molecules and then inhibit the expression of APC2. This molecule can also inhibit the expression of DKK1 through the HIF-1α-dependent pathway through miR-146a and finally activate the WNT/β-catenin pathway [31]. In addition, studies have found that the NOX1-ROS-NRX

pathway can affect β-catenin degradation, which can further affect NIS transport [32, 33].

Other molecules target the PM NIS for transport, degradation, and inactivation

ADP-ribosylation factor 4 (ARF4) is responsible for NIS transport from the Golgi to the PM [34]. Valosin protein (VCP) is a key component of endoplasmic reticulum-associated protein degradation (ERAD), which is involved in the intracellular processing of NIS. VCP can increase NIS proteolysis, thereby reducing NIS transport to the PM [35]. Therefore, decreased expression of ARF4 and increased expression of VCP in PTC can lead to decreased PM-targeted transport and increased degradation of NIS, which may ultimately be manifested as decreased sensitivity to RAI. In addition, although most membrane proteins are functionally regulated by dimerization, there is little definitive evidence for NIS dimerization, and whether this affects RAI uptake and treatment success is not fully understood. Fortunately, Thompson, Rebecca J et al. demonstrated for the first time that NIS dimerized in vitro, residues Y242, Y243, and Q471 were associated with dimerization, and single mutations of residues Y242 and T243 prevented NIS from playing its role. However, silencing of Q471 does not affect the absorption of RAI [36]. If subsequent studies prove that dimerization of NIS is critical for its transport to the PM, knowledge of the molecular mechanism of RAIR-DTC will be further improved.

The molecular mechanisms of NIS expression

Epigenetics and NIS expression

How does m6A affect NIS expression?

The expression of the m6A regulator insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) was significantly increased in PTC patients (patients with lymph nodes or distant metastases) and was significantly associated with decreased NIS expression. RUNX2 (Runt-related transcription factor 2) can bind to the NIS promoter and inhibit NIS transcription. Studies have confirmed that IGF2BP2, the only gene associated with disease-free survival (DFS) of PTC, can be associated withRUNX2. Binding to the m6A modification site of the 3′-UTR of RUNX2 mRNA subsequently increases the stability of the latter mRNA, so IGF2BP2 can affect NIS transcription by binding to RUNX2 [37, 38].

How does acetylation affect NIS expression?

Histone acetylation is involved in the regulation of transcriptional activity, and gene transcription can be silenced when histone deacetylation occurs [39]. The BRAFV600E mutation increases global histone acetylation in DTC cells, but it leads to deacetylation of histones at the NIS promoter, thereby silencing NIS expression. The combination of the BRAFV600E inhibitor PLX4032 (vemurafenib) and the histone deacetylase inhibitor SAHA (vorinostat) increased RAI uptake and thyroid-associated transcription factor expression in BRAFV600E mutant TC cells [40, 41]. In addition, H4 histone acetylation of the transcription coactivators TAZ, PAX8 (paired box gene 8), NKX2-1 (NK2 homeobox 1) NIS, TSHR and TG with PDZ binding motifs can regulate the differentiation process of thyroid cells [42].

How does methylation affect NIS expression?

DNA methylation usually silences gene expression, the CpG islands are mainly located in the promoter region of the gene. However studies have shown that there is no quantitative relationship between the CpG-island1 methylation level of the NIS proximal promoter and the NIS mRNA expression level [43]. However, DNA methylation of NISCpG-island2 (named NIS distal enhancer (NDE) due to its enhancer activity) was correlated with decreased NIS expression levels [44].

In addition, The TSHR (thyroid stimulating hormone receptor) promoter is silenced due to high methylation in DTC, and the decreased expression of TSHR can affect the response of cancer cells to TSH and then affect the response of NIS to TSH, which may ultimately lead to the decreased sensitivity of cancer cells to RAI [45]. In addition, studies have found that TSHR methylation is significantly correlated with BRAFV600E gene mutation [46]. Therefore, BRAF V600E may be one of the factors causing TSHR methylation, which further affects NIS expression by affecting TSHR methylation.

Post-translation regulation and NIS expression

How does glycosylation affect NIS expression?

NIS is highly glycosylated in the membrane. Previous studies have shown that the NIS glycosylation status affects NIS expression and NIS fine cell membrane localization in hNIS/tdTomato-transfected HeLa cells. When NIS is glycosylated, NIS expression and NIS cell membrane localization increase, and when the degree of glycosylation is low, the number of membrane-localized NIS proteins decreases compared with that of completely glycosylated proteins [47] In general, PIGU can lead to NIS glycosylation, affecting NIS expression and cell membrane localization. Amit and Moran et al. found that the expression of PIGU [one of the components of the glycosyl phosphatidylinositol aminositol transaminase (GPIT) complex] was reduced in PTC patients, which may lead to insensitivity to RAI treatment in PTC patients. However, the authors did not study the exact mechanism by which PIGU affects NIS activity [48]. In addition, Zhang and Li et al. found that

curcumin can promote NIS expression and membrane localization by enhancing NIS glycosylation, which can increase RAI uptake by PTC cells, indicating its potential for the treatment of RAIR-DTC [49].

How do other molecules affect NIS expression?

CREB3L1 is a transcription factor located in the endoplasmic reticulum, where its N-terminal domain is transferred to the nucleus after interaction with proteolytic enzymes in the Golgi. CREB3L1 overexpression increased NIS levels in FRTL5 cells, CREB3L1, a downstream effector of thyroid stimulating hormone (TSH), was upregulated in thyroid follicular cells, and the latter regulated NIS transcriptional expression in response to TSH stimulation. Therefore, the expression level of CREB3L1 in TC cells can affect the expression level of NIS [50].

Studies have shown that transcription coactivator with PDZ binding domain (TAZ) is involved in the Hippo pathway, PAX8 is a positive regulator of NIS expression, TAZ expression is increased in TC cell lines, and TAZ can negatively regulate Pax8 transcriptional activity in the NIS promoter. Therefore, TAZ can act as an auxiliary repressor of PAX8 to regulate Slc5a5 expression in TFC [51, 52]. PBF inhibits NIS enhancer activity through the human upstream enhancer element (hNUE) and subsequently affects NIS transcription [53].

Other studies have found that mTOR phosphorylation preferentially activates the mTORC2 complex and its downstream factor AKT-Ser473 rather than mTORC1 in PTC, especially BRAFV600E mutant PTC, and inhibition of mTORC2 can increase NIS mRNA expression. However, inhibition of mTORC1 had no effect on NIS mRNA expression, indicating that mTORC2 could affect NIS expression. However, the effect of the BRAFV600E mutation on the low expression of mTORC2 and NIS mRNA was not further examined in the study [54].

The TGF-β1/SMAD pathway plays an important role in autophagy gene expression. Downregulation of Rap1GTP-activating protein (Rap1GTP) expression in PTC can downregulate NIS mRNA and protein expression through the TGF-β1/SMAD3 signaling pathway, but this result has only been verified in single cell lines and needs to be supplemented by other tests [55]. Another study found that the BRAF V600E mutation was associated with low expression of Rap1GTP mRNA, and studies confirmed that miR-3121-3p could bind to the Rap1GTP promoter and inhibit its expression, which may subsequently activate the MAPK/ERK pathway and play a role [56] (Fig. 2).

How do autophagy and ROS affect NIS?

A basic introduction to autophagy

Autophagy forms autophagic vesicles by phagocytosis of proteins or organelles in the cytoplasm and then fuses with lysosomes to form autophagic lysosomes to degrade phagocytic substances. Finally, the degraded substances are released, and the released substances can be used again for metabolic needs or the renewal of some organelles. Autophagy is usually divided into microautophagy, chaperone-mediated autophagy, and macroautophagy. The autophagy mentioned in this paper is usually macroautophagy, which is a multistep process usually composed of 7 steps, among which autophagy-related genes (ATGs) are usually involved in steps 1–5, and genes common to other lysosomal pathways are usually involved in steps 6–7. Briefly, the autophagy process includes nucleation/initiation, elongation, maturation and degradation of components and membrane compartment recycling. In the nucleation stage, the ULK complex (mainly composed of ULK1, ATG13 and FIP200) is activated. In the initial stage, VPS34 binds to Beclin1 and induces the formation of phagocytic vesicles. The ATG7-ATG3 and ATG5-ATG12 ubiquitin systems convert microtubule-associated protein 1 light chain 3 (LC3-I) to microtubule-associated protein 2 light chain 3(LC3-II) in the extension stage. LC3 on the outer membrane of autophagy can bind to cargo by its LC3 binding motif and mediate selective autophagy. When the cargo is completely isolated into autophagosomes, autophagosomes begin to mature and form autophagosomes with lysosomes to degrade cargo proteins. Autophagy ends when degradation products are released back into the cytoplasm to be reused by cells [12, 13, 57]. Selective autophagy is related to various pathological conditions of cancer [58], but autophagy plays a double-edged role in cancer, as it can not only inhibit cancer occurrence but also promote cancer occurrence. Ganzleben, Ingo et al. have made a detailed review on the role of autophagy in cancer [12].

How does autophagy affect NIS?

Autophagy regulates iodine uptake in TC by affecting NIS degradation [14]. Autophagy activated by different pathways in DTC may degrade NIS through autophagosomes. The activation of autophagy under different conditions will be discussed below, and the molecules involved in these conditions may indirectly lead to the production of RAIR-DTC through autophagosomes.

LC3 can bind to a variety of proteins for autophagic function. Through interaction with a series of autophagic

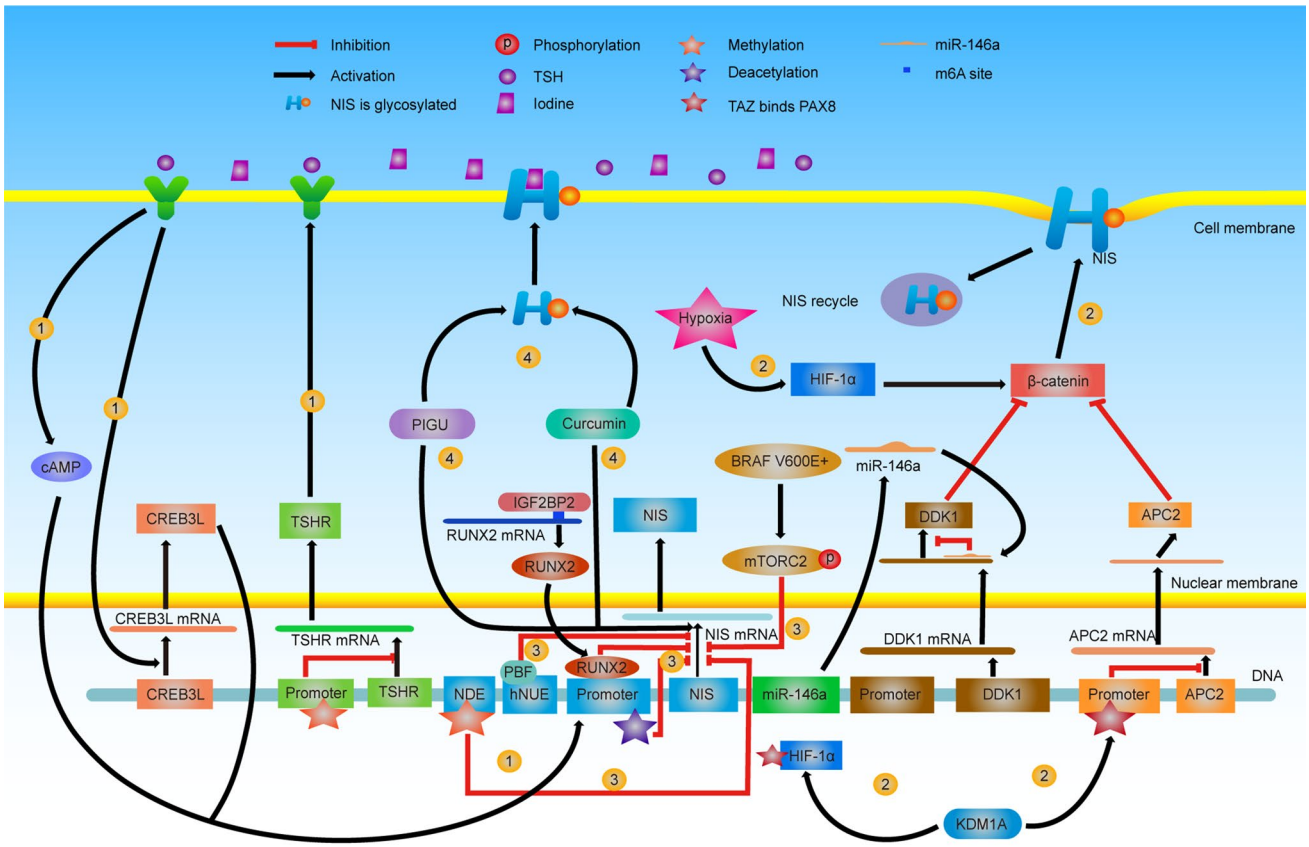

Fig. 2 Pattern of NIS expression and recovery in DTC cells. (1) TSH usually binds to TSHR to activate downstream signals and promote the expression of CREB3L. CREB3L may act together with cAMP in the hNUE region of the NIS gene to promote NIS expression. When the promoter of the TSHR gene is methylated, TSHR expression is inhibited, thus affecting NIS expression. (2) DDK1 and APC2 are negative regulators of β-catenin and promote β-catenin degradation through ubiquitination. When KDM1A is increased in cells, it can promote APC2 promoter deacetylation and HIF-1α deacetylation and then inhibit the expression of DDK1 and APC2. The degradation of β-catenin decreased, and NIS recovery increased. Hypoxia can also activate HIF-1α and then inhibit β-catenin degradation, resulting in increased NIS recovery. (3) NDE methylation in the NIS gene; PBF acts on hNUE; PAX8 binds to TAZ; promoter binding of RUNX2 and activation of mTORC1 by BRAFV600E inhibited NIS gene expression. IGF2BP2 can bind to RUNX2 mRNA methylation sites to stabilize RUNX2 translation. (4) When NIS is expressed on the plasma membrane, it is in a glycosylated state, and the impaired glycosylation state of NIS may cause it to remain in the cytoplasm. PIGU and curcumin can promote NIS glycosylation and NIS expression, which have potential as new therapeutic targets

proteins, the newly synthesized LC3 (LC3-I) becomes the autophagic membrane form (LC3-II) to promote membrane expansion and closure [59]. LC3-I exists diffusely in the cytoplasm, and LC3-II is confined to the cytoplasm and the surface of autophagic vesicles. Studies have found that RAI uptake in nonmyelinary thyroid cancer (NMTC) is associated with LC3-I and LC3-II. In NMTC patients with good RAI uptake, LC3-I expression was increased, and the number of LC3-II-positive lattices was increased. Moreover, membranous NIS expression was decreased in tumor cells with low autophagic activity, and membranous NIS expression was found in tumor cells with a significantly increased LC3-II-positive lattice, but LC3-I expression was not correlated with membranous NIS expression [60].

AMPK and mTORC1 are a pair of key molecules involved in autophagy regulation, which can play a role by regulating downstream ULK1, TFEB and other molecules. Studies have found that the expression and activity of AMPK are significantly increased in papillary thyroid cancer, and AMPK can be activated to significantly induce the degradation of NIS protein through the autophagy-lysosomal pathway and finally reduce the uptake of RAI by cells [61]. Another study found that PLX4720, a BRAFV600E inhibitor, induced protective autophagy and subsequently reduced the efficacy of the drug. PLX4720 downregulates BRAFV600E and subsequently activates LKB1-AMPK signaling and reduces mTOR activity through a MEK/ERK-dependent mechanism. AMPK activation can activate ULK1 through the AMPK-ULK1 pathway to

induce autophagy but does not require the inhibition of mTOR to increase autophagy. The study did not further investigate whether PLX4720 may induce autophagy by other means, so this conclusion may be affected by other factors [62]. Transcription factor E3 (TFEB) plays a key role in regulating autophagy and lysosomes [63]. mTORC1 phosphorylates the S211 residue of TFEB, which then interacts with the adaptor protein YWHA/14-3-3 in the cytoplasm and remains in the cytoplasm, thus inhibiting nuclear ectopic activity. When cells are starved, calcineurin can dephosphorylate TFEB, dissociate it from adaptor proteins, and enter the nucleus to regulate the transcription of relevant target genes [64]. In addition, AMPK-mediated phosphorylation of TFEB and mTORC1-mediated TFEB are required for autophagic regulatory protein activity under starvation. The transcriptional activity of TFEB is mainly regulated by AMPK, while the nuclear ectopic activity of TFEB is determined by mTORC1. In addition, AMPK and mTORC1 can directly regulate the phosphorylation of ULK1 to regulate autophagy regardless of the cellular nutrition status. However, due to the different phosphorylation sites, the effects on ULK1 activity and autophagy are also different [65]. Another study found that nuclear ubiquitination of coactivator-associated arginine methyltransferase 1 (CARM1) decreased and its content increased in glucose-starved cells. Studies have confirmed that the AMPK-FOXO3-SKP2-CARM1-TFEB pathway can induce autophagy and play corresponding roles [66]. Epigenetic inhibition of hepatic autophagy after feeding is mediated by SHP-KDM1A/LSD1/TFEB [67]. At the epigenetic level, histone deacetylase inhibitors such as SAHA-induced TEFB acetylated lysosomes to affect TFEB nuclear ectopic activity and transcriptional activity independently of the mTORC1 process, ultimately inducing autophagy and promoting lysosome function. This study also proposed that TFEB phosphorylation regulates the mode of action of TFEB acetylation regarding the direct effect of TFEB phosphorylation on TFEB acetylation. Unfortunately, this mode of action was not confirmed in this study, and additional studies are needed to clarify whether this mode of action exists [68]. Therefore, molecules that regulate TFEB transcriptional activity and nuclear ectopic activity may be involved in autophagic regulation in an indirect way, and nutrient deficiency is often present in solid tumors [69], so when DTC cells show nutrient deficiency, autophagy may be activated through the above pathways. Notably, TERT acts as an upstream regulator of mTORC1 activity. In TC with TERT promoter mutation, NIS mRNA expression may be decreased [70], while HIF-1α can bind to the TERT promoter under hypoxia and promote an increase in TERT expression, which subsequently inhibits mTOR and induces autophagy, enabling PTC cells to survive under hypoxia [71].

BRAFV600E gene mutation can affect autophagy through WT1, Wilms' tumor 1 (WT1) encodes transcription factors, which are involved in the regulation of cell survival, proliferation and differentiation as both oncogenes and tumor suppressor genes in a variety of malignant tumors. The expression of WT1 in PTC tissues, especially BRAFV600E-mutated PTC tissues, is significantly increased, and the higher the expression of WT1 is, the shorter the survival time of patients is. Silencing WT1 expression can significantly inhibit the AKT/mTOR and ERK/P65 signaling pathways in BRAFV600E-positive PTC cells and lead to changes in the autophagy-related proteins P62, LC3A/B, and ATG5/7 and the apoptosis-related proteins caspase 3, BAX and Bcl2. However, the limitations of this study are that most of the data are from TCGA database, and there was no further verification. Moreover, WT1 has not been further shown to specifically regulate the autophagy and apoptosis pathways in cancer cells, which suggests a direction for future research [72] (Fig. 3).

Foxp3 is a member of the forked head transcription factor family and is considered to be the signature molecule of regulatory T cells (Tregs). Foxp3 plays a key role in the regulation of immune autostability in the body. It is not only the signature molecule of CD + 4 CD + 25 Tregs, but also determines the function of these Tregs. microRNAs (miRNAs) in cells are a group of short, non-coding regulatory Rnas that target mRNA for cleavage, leading to translation inhibition. Mirnas are involved in many biological processes, including autophagy, inflammation, cell cycle regulation and so on. The activation of autophagy in cells has a double-edged sword effect, and the relationship between miRNA, Foxp3 and autophagy is also different in different cancer species. Zheng et al. confirmed that miRNA can activate autophagy in cells by inhibiting Foxp3. For example, in patients with allergic rhinitis (AR), miR-125b can induce airway epithelial autophagy and cause epithelial cell dysfunction by inhibiting FoxP3 expression, thus participating in the pathogenesis of AR [73]. Li et al. confirmed in gastric cancer cells that mir-133a-3P can promote the proliferation and autophagy of gastric cancer cells by inhibiting Foxp3, leading to the development of gastric cancer [74]. However, Wang et al. demonstrated that miR-125b inhibits FoxP3 and activates autophagy in FTC, thereby enhancing the sensitivity of RAIR-DTC to cisplatin or sorafenib [75]. In discussing the relationship between Foxp3 and autophagy, song et al. confirmed that Beclin-1, a protein associated with autophagy, is a favorable prognostic factor for gastric adenocarcinoma, which is related to the increase in the number of infiltrating Tregs and the expression of FOXP3 in tumors with tumor inhibitory function [76]. Another study demonstrated for

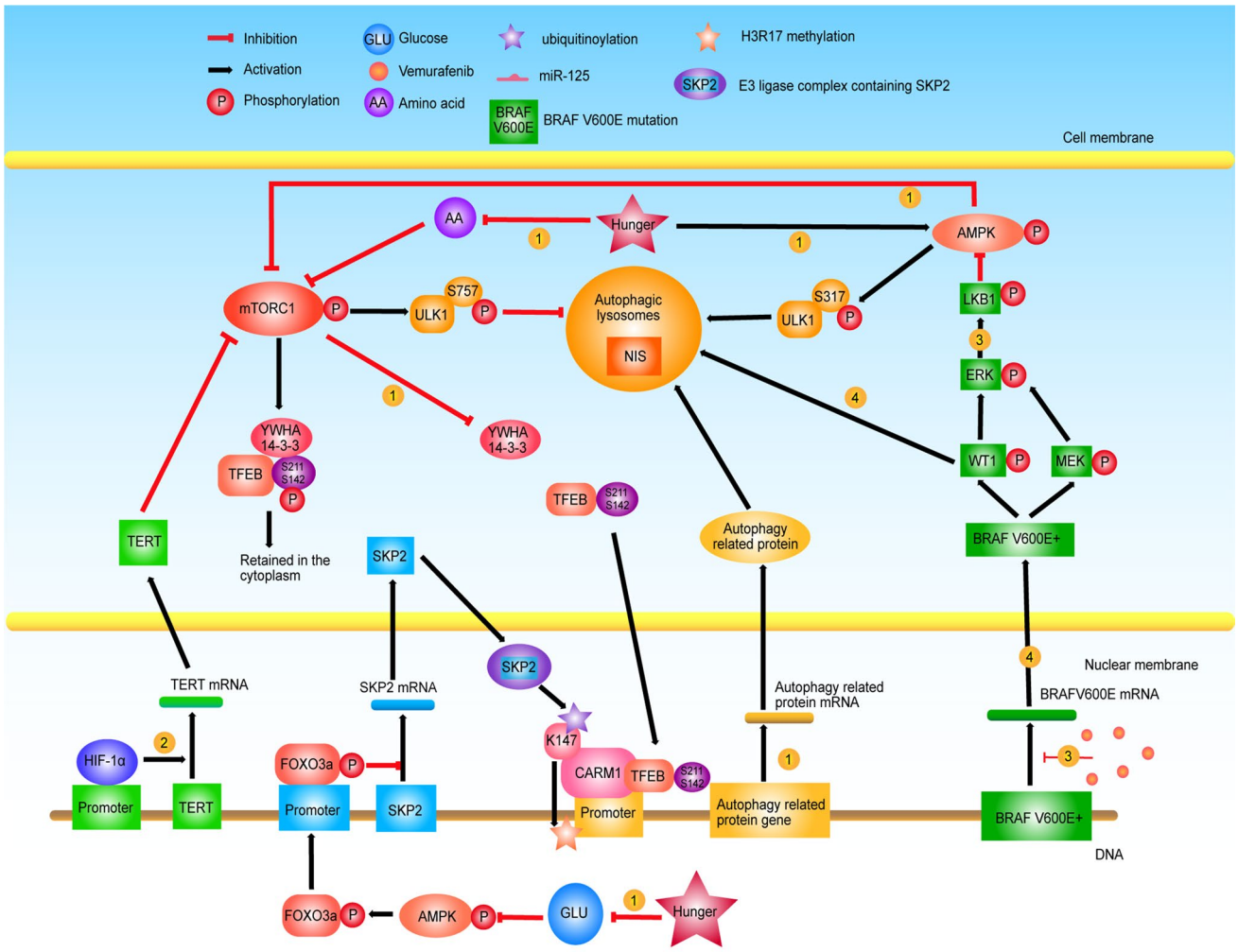

Fig. 3 Relationship between autophagy and NIS in DTC cells. NIS can be degraded by autophagic lysosomes, and the activation of the autophagy pathway in DTC cells may further lead to increased NIS degradation. (1) In general, mTORC1 can induce the phosphorylation of the ULK1 S757 residue to inhibit its activity and promote the phosphorylation of the S211 and S142 residues of TFEB to bind to the chaperone YWHA-14-3-3 and remain in the cytoplasm, ultimately inhibiting autophagy. AMPK can induce the phosphorylation of ULK1 S317 and other residues to activate its activity. This change in turn promotes autophagy. In DTC cells, the amino acid content decreases under starvation, mTORC1 can directly sense the change in amino acid content, and mTORC1 activity is inhibited, which reduces the phosphorylation of downstream proteins. TFEB and chaperone proteins dissociate and enter the nucleus to play a role. Moreover, starvation activates AMPK, which activates ULK1 and inhibits mTORC1 activity. AMPK in the nucleus activates FOXO3a, which can inhibit SKP2 expression. SKP2 is involved in CARM1 ubiquitination-induced degradation, and SKP2 inhibition reduces CARM1 degradation. The latter, together with TFEB, promotes the expression of autophagic lysosomal-related genes, and finally, autophagy is activated through the above process. (2) HIF-1α promotes the expression of TERT by binding to the TERT gene promoter and then inhibits the activity of mTORC1 and promotes the activation of autophagy. (3) The application of vemurafenib in the treatment of RAIR-DTC with the BRAF V600E mutation can activate AMPK and activate autophagy by inhibiting the reduction in LKB1 activity. (4) BRAFV600E mutation can increase WTI and the latter can induce autophagy

the first time that inhibition of autophagy can control the expression of stage-specific TIL, promote the upregulation of CD4, FoxP3 TILs, and increase the susceptibility of lung cancer to carboplatin in advanced lung cancer [77]. The TGF-β1/SMAD pathway also plays an important role in autophagy, Increased FOXP3 expression was found to be accompanied by decreased NIS expression in PTC, suggesting thatFOXP3 2qzexpression may affect NIS expression and ultimately render patients insensitive to RAI treatment. Further studies found that FOXP3 expression in PTC may reduce the expression of NIS transcripts and the targeted transport of NIS PM by activating TGF-β1/SMAD, but this study did not exclude the influence of other factors. The specific relationship between FOXP3, TGF-β1 and NIS expression still needs to be further elucidated in subsequent studies [75, 78].

How do ROS affect NIS?

Studies have found that in HT29NIS cells, hypoxia and quiescent cells both cause abnormal NIS expression and NIS cell sublocalization [79]. TGF-β1/SMAD3 regulates ROS expression as an upregulated pathway for ROS. TGF-β1 can affect the ability of cancer cells to take up iodine in TC patients. TGF-β1 is significantly activated in tumor invasion areas and can negatively regulate the expression of NIS, affecting the sensitivity of TC cells to iodine therapy, which is ultimately reflected in the improvement of iodine tolerance in patients [8]. Other studies have found that ROS levels are increased in PTC, and ROS levels are directly related to NIS regulation. ROS in PTC are mainly catalyzed by the NADPH enzyme, and NOX4 is one of the types of NADPH enzymes. NIS may regulate NIS transcription levels, NIS cell membrane localization and NIS activity and eventually inhibit NIS. However, the mechanism by which ROS inhibit NIS is still unclear [15]. Research have found NOX4 and its chaperone P22phox are upregulated in TC cells such as PTC [80]. Starvation and BRAFV600E mutations are identified in NOX4 and ROS expression regulated by TGF-β1/SMAD3.

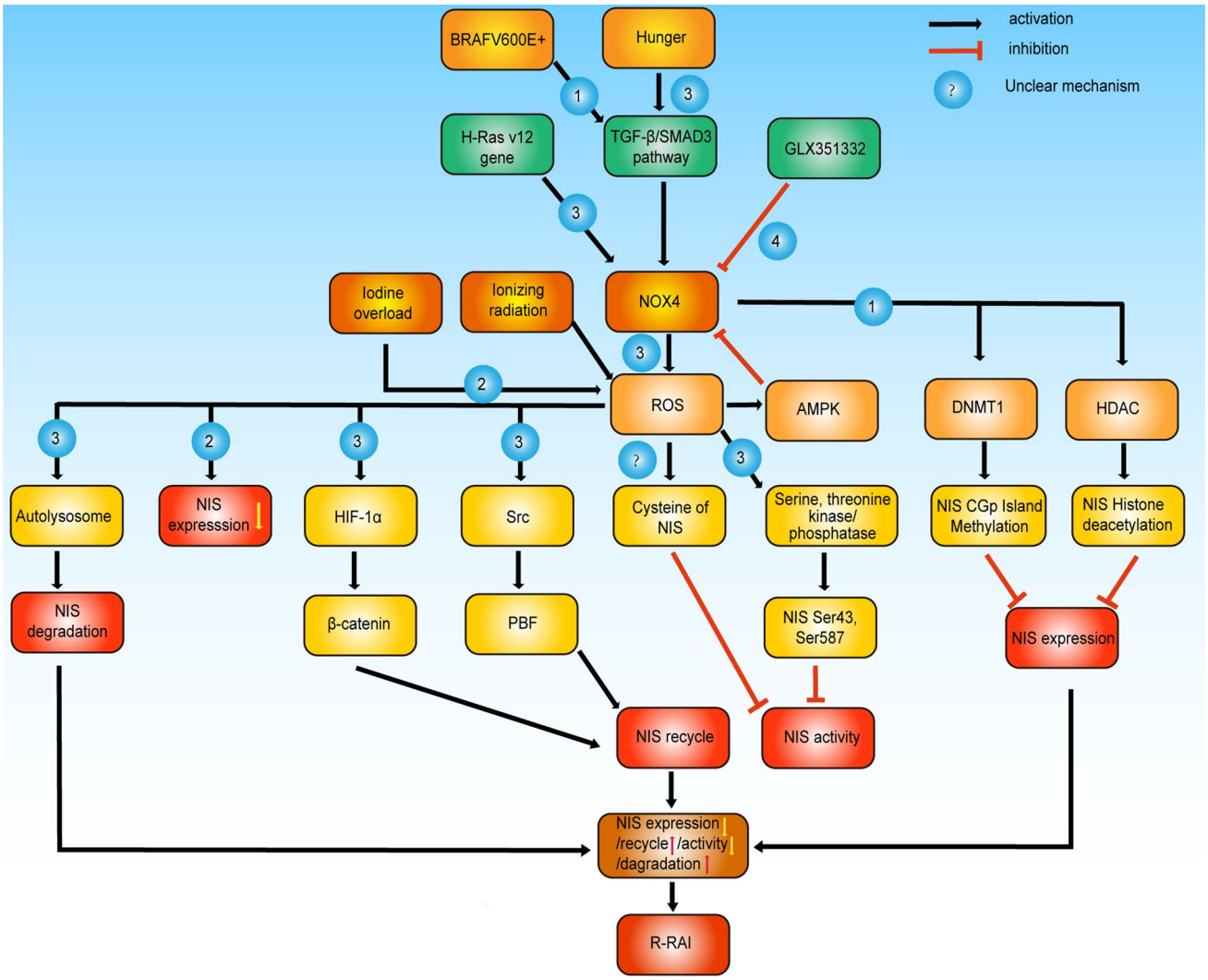

Fig. 4 The role of ROS in RAIR-DTC. (1) In DTC cells with the BRAF V600E mutation, the effect of BRAF V600E protein on NIS's CpG island methylation and NIS histone deacetylation may be achieved through TGF-β/SMAD3 pathway activation of NOX4, which further activates DNMT1 and HDAC, ultimately leading to decreased NIS expression. (2) Iodide overload may lead to a time-dependent decrease in NIS expression in DTC cells. (3) Starvation and the H-RAS-V12 gene can activate NOX4, which further promotes ROS production. ROS may affect NIS through autophagic lysosomes, Src, HIF-1α, NIS cysteine residues, and tyrosine kinase/phosphatase, eventually causing R-RAI. (4) The NOX4 inhibitor GLX351322 can inhibit NOX4 and then affect its downstream targets, which is a potential therapeutic target for RAIR- DTC

Under starvation conditions, NOX4 expression can be upregulated through the TGF-β1-SMAD3 pathway, which can then activate ERKS and PI3K/AKT to regulate cell apoptosis and increase ROS content so that NOX4 can play a role in glycolysis. PTC cells are not sensitive to treatment with lenvatinib, and the combination of lenvatinib and the NOX4 inhibitor GLX351332 can significantly reduce cell viability [81]. In addition, ROS can activate AMPK, which inhibits NOX4 expression [82]. Studies have proven that in PTC with the BRAFV600E mutation, BRAFV600E induces functional TGF-β1 production through the MEK-ERK-dependent pathway and subsequently induces ROS production through the TGF-β1/SMAD3/NOX4/ROS pathway, and finally, ROS cause a reduction in NIS expression levels [83] (Fig. 4).

How does the interaction between autophagy and ROS affect NIS?

Many studies have explored the relationship between autophagy and ROS. Autophagy can not only remove oxidized/damaged proteins, but also restrict the production of ROS by removing the organelles that produce ROS (such as mitochondria and peroxisome). The regulation of ROS on autophagy can run through the entire process of autophagy. Different concentrations of ROS can regulate autophagy in different ways, usually activating the production of autophagy, but sometimes it may inhibit autophagy [84]. In addition, the mode of action between autophagy and ROS has been discussed in a variety of diseases (including tumors). For example, qin et al. confirmed that in gastric cancer with autophagy loss, loss of autophagy leads to increased intracellular ROS levels and mitochondrial ROS levels, and then activates HIF-1α through ros-NF-κb-HIF-1α pathway and induces EMT. The malignant phenotype of gastric cancer cells was transformed [85]. Kaminskyy demonstrated that inhibiting autophagy in non-small cell lung cancer can improve the killing efficiency of drugs such as cisplatin by increasing ROS formation [86]. The relationship between ROS and autophagy in RAIR-DTC can be summarized as follows: ROS itself can directly regulate and participate in the regulation of NIS content, or indirectly regulate NIS content as the upstream of the autophagy pathway, and it plays an intermediate hub role in this process. The relationship between ROS and autophagy in RAIR-DTC can be summarized as follows: (1) HMGB1, which is mainly located in the cell nucleus and binds to chromatin to stabilize its structure, can shuttle from the nucleus to the cytoplasm under various stress conditions, including excessive ROS production. In thyroid cancer cells, HMGB1 expression is upregulated, and starvation stimulation induces ROS production. It has been demonstrated that ROS can cause HMGB1 to translocate from the nucleus to the cytoplasm, and HMGB1 plays a crucial role in the process of ROS increase induced by starvation. HMGB1 entering the cytoplasm can lead to the phosphorylation of AMPK, mTOR, and P70S6K, further promoting the formation of autophagosomes and ultimately resulting in the degradation of NIS and reduced RAI uptake [87, 88]. (2) Studies have found that ROS [89], hypoxia [90] and other conditions can induce ERS. Endoplasmic reticulum stress (ERS) is associated with the activation of autophagy in cells. ER stress activates autophagy through the unfolded protein response (UPR), which upregulates autophagy-related genes and regulates LC3-I. Studies have found that conditions such as ROS and hypoxia can induce ERS. ROS activate the PERK/eIF2α/ATF4/CHOP pathway to activate autophagy, where ATF4 not only regulates the expression of CHOP but also forms dimers with CHOP to jointly regulate the expression of autophagy-related genes. Prolonged ERS can also activate the ER oxidoreductin 1α (ERO1α), which subsequently regulates autophagy and other processes through the endoplasmic reticulum calcium release channel IP3R1/Calmodulin-dependent protein kinase II (CaMMII)/NOX2/ROS [89–93]. Notably, Yang et al. associated the above process with autophagy in PTC cells through SIRT6, providing evidence of ERS-induced autophagy in PTC cells. SIRT6 is a nuclear histone deacetylase that acts on the lysine 56 acetylation (H3K56ac) and (H3K9ac) sites of histone H3. In his study, it was found that SIRT6 was overexpressed in PTC, and Belin1 mRNA and protein, ATG mRNA, VPS34 mRNA, LC3II/I and so on were increased. In addition, ROS overexpression of SIRT6 was increased in PTC cells. Finally, the authors found that SIRT6 could induce autophagy in PTC cells through the NRROS/NOX2/ROS/ERS pathway [94]. (3) In papillary thyroid carcinoma (PTC), estrogen (E2) may be associated with the incidence as in 2020, the age-standardized incidence rate of PTC was 101/100,000 in females and 3.1/100,000 in males. Additionally, the age-standardized mortality rate was 0.5/100,000 in females and 0.3/100,000 in males, indicating a significantly higher incidence rate of PTC in females compared to males. Estrogen receptors (ER) are divided into nuclear receptors and membrane-related receptors, including ER-α and ER-β subtypes. ER-α is generally associated with disease progression, whereas ER-β exhibits the opposite effect. Interestingly, both receptor types are expressed in PTCs, but E2 can promote the expression of ER-α and it has been observed that the expression of ER-α is increased in PTC cells. Subsequently, researchers demonstrated that E2 activates reactive oxygen species (ROS) and the MEK/ERK signaling pathway in an ER-α-dependent manner. They further discovered that ROS can partially activate the MAPK pathway, which subsequently enhances autophagy in PTC cells. This finding provides further insight into

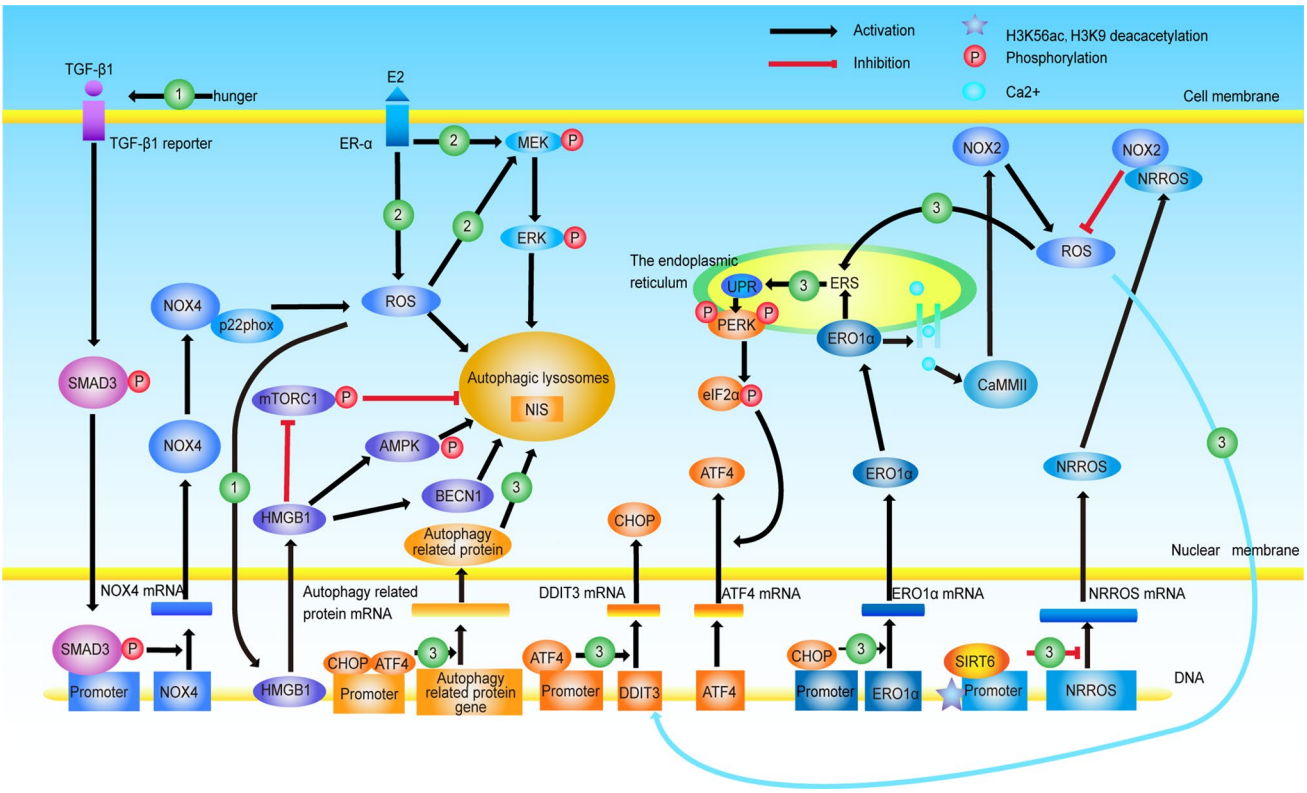

Fig. 5 Effects of the interaction between ROS and autophagy on NIS in PTC cells. (1) When PTC cells are in a starvation state, NOX4 expression can be promoted through the TGF-β/SMAD3 pathway, which promotes ROS production, which can transfer HMGB1 from nuclear ectopic expression to the cytoplasm. HMGB1 in the cytoplasm can promote AMPK and BECN1 to induce autophagy by inhibiting mTORC1. (2) Estrogen promotes autophagy by activating the MEK/ERK pathway and ROS through estrogen receptor α. ROS can also activate MEK to a certain extent and ultimately promote NIS degradation. (3) RERS plays an important role in the activation of autophagy. Increased expression of SIRT6 in PTC can inhibit the expression of NRROS and promote the production of ROS by NOX2. Subsequently, ROS can pass through the ERS pathway, namely, the PERK/eIF2α/ATF4/CHOP pathway, which further activates autophagy. In addition, the long-term ERS factor CHOP can promote the expression of ERO1α. On the one hand, ERO1α can promote ERS, and on the other hand, ERO1α can regulate NOX2 activity through IP3R1/CaMMII, thus causing an increase in ROS. ROS can finally promote the expression of the CHOP gene, forming a positive feedback effect

the relationship between autophagy and ROS in PTC. It is noteworthy that variable splicing occurs in ER, resulting in different transcripts and translation of distinct ER isoforms such as ER-α66, ER-α46, ER-α36, and ER-β1-5. Variable splicing can lead to incomplete functional domain structures in ER isoforms, thus affecting their functions. Therefore, studying the expression and role of different ER isoforms in PTC is also crucial [95–98]. In summary, the relationship between ROS and autophagy in RAIR-DTC involves the HMGB1-ROS-autophagy pathway, ERS-ROS-autophagy pathway and ER-ROS- autophagy pathway. Activation and interaction of these pathways contribute to increased autophagy in RAIR-DTC, leading to reduced sensitivity of thyroid cancer cells to RAI uptake. These findings provide important insights into the pathogenesis of RAIR-DTC and the identification of potential therapeutic strategies (Fig. 5).

Importance of the interaction between autophagy and ROS in RAIR-DTC

In conclusion, different molecules can affect autophagy or ROS in direct or indirect ways. Based on the relationship between autophagy and NIS or ROS and NIS, these molecules may indirectly participate in NIS regulation by activating autophagy, indirectly activate ROS production to participate in NIS regulation, or affect NIS by regulating ROS and the autophagy pathway. Through the interaction between pathways and molecules, the network-like regulation of NIS by these molecules can be further inferred. Unfortunately, there is no direct evidence to demonstrate the relationship between these molecules and NIS, so further exploration of the relationship between them or their roles in RAIR-DTC is still urgently needed. Therefore, further elucidation of the pathogenesis of RAIR-DTC may still be the focus of future research.

The tumor microenvironment and RAIR-DTC

The immune system plays a key role in tumor development, and when tumor immune surveillance is disrupted, tumorigenesis and cellular homeostasis are promoted. The tumor system is involved in three basic stages of tumor formation: elimination, balance and escape. In the elimination stage, newly developed cells can be recognized and destroyed by immune cells such as NK cells and cytotoxic CD8 + lymphocytes. In the equilibrium phase, the immune system generates a kind of pressure, the tumor cells will mutate, and the mutated tumor cells will be able to evade immune surveillance. During the escape phase, tumor variants that can escape the immune system emerge, eventually leading to tumor growth. The study found that in the TC tumor microenvironment (TME), which includes myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), an increase in MDSCs is associated with poor prognosis. MDSCs can be differentiated into mature myeloid cells by tyrosine kinase inhibitors, and their function is inhibited. NK cells, T cells (CD4 + T cells, CDT cells, Treg cells, Th17 cells) and mast cells are also present in the TME, among which PD-1 expression is related to CD8 + and CD4 + T cells infiltrated by TCs [99, 100]. The role of tumor-associated macrophages in TC has been thoroughly reviewed by Liu, Qi et al. [101]. Using subcutaneous HT29NIS and K7M2NIS tumors, Castillo-Rivera and Fabio et al. demonstrated that tumor cells in hypoxic and quiescent environments impaired NIS expression and iodide uptake at the PM and showed that the TME plays a key role in the successful treatment of NIS-based cancers [79]. The complexity of the TME suggests that exploring the interactions among microenvironmental factors, signal transduction, and metabolic pathways could help elucidate the pathological mechanisms involved in NIS-mediated therapy.

Targeted therapy of RAIR-DTC

Various reviews have covered the management of patients with RAIR-DTC [102, 103]. The treatment of advanced RAIR-DTC is an urgent problem to be solved. The timing of using kinase inhibitors in RAIR-DTC patients [104] and the clinical indications [105] have been discussed. Currently, tyrosine kinase inhibitors, such as sorafenib and lenvatinib, have been approved by the FDA for use in RAIR-DTC, which improves progression-free survival but has no effect on overall survival [105]. So far, a study has evaluated the clinical efficacy and safety of lenvatinib and sorafenib as first-line treatment in the actual practice of distant metastasis or locally advanced, progressive, RAIR-DTC. This study found that lenvatinib was associated with longer PFS in Asian patients, but with a higher frequency of severe hypertension and albuminuria than sorafenib [106], although another study showed that lenvatinib dose reduction triggered by an emergency adverse event did not result in lenvatinib's efficacy in treating RAIR-DTC. Conversely, continued use of a reduced dose of Lenvatinib and a low rate of serious adverse events may contribute to favorable outcomes [107]. Suzuki, K et al. discussed the synergistic anti-tumor effect of lenvatinib and RAI, and found that combined therapy could be used as postoperative ablation therapy for high-risk DTC or as an alternative therapy for adjuvant RAI and high-dose RAI for metastatic thyroid cancer, but the combined therapy did not increase RAI uptake. Clinical application may require the use of drugs that enhance NIS function and RAI uptake in conjunction with this combination regimen [108]. September 17, 2021, cabozantinib was also approved by the FDA for the treatment of adults and pediatric patients 12 years of age and older with locally advanced or metastatic DTC who have progressed after previous VEGFR-targeted therapy and who are refractory or ineligible for RAI [109]. The role of microRNA (miRNA) in fine-tuning gene expression has become a major regulatory mechanism for the occurrence of developmental and pathological processes. Both mature products of miR-146b (miR-146b-5p and -3p) are among the most richly expressed miRNAs in tumors. Selumetinib, a mitogen-activated protein kinase (MEK) inhibitor, has a clinically significant increase in iodine uptake and retention in RAIR-DTC; In particular, the effectiveness may be higher in patients with RAS mutation disease. It was first found to restore NIS transcripts by inhibiting its associated targeted mirnas, such as has-miR-146b-5p, has-miR-146b-3p and has-let7f-5p, resulting in increased uptake and retention of RAI in RAIR-DTC patients. Another study further clarified the relationship between miR-146b-3p and NIS: Mir-146b-3p binds to PAX8, NIS untranslated regions, resulting in impaired protein translation and subsequent reduced iodide uptake. Moreover, miR-146b and PAX8 regulate each other and share common target genes. Therefore, inhibition of Mir-146b-3p can restore NIS transcripts. Some scholars have proposed whether selumetinib added to the initial RAI treatment can improve the complete response (CR) rate of DTC patients with a high risk of first-stage treatment failure according to postoperative pathological risk stratification. Unfortunately, although selumetinib can improve iodine intake in RAIR-DTC patients, compared with radioiodine alone, selumetinib adjuvant RAI does not improve CR in patients with differentiated thyroid cancer (DTC) at high risk of initial treatment failure, that is, selumetinib does not optimize the treatment of such patients [110–113].

In a word, although some kinase inhibitors have been officially approved for use, researchers are still exploring

Table 1 Application of different kinase inhibitors in RAIR-DTC

Drug	Research	Cancer	Outcomes	Adverse reaction	Cite
Anlotinib	–	RAIR-TC	PR[a], Tg[b]	HFSR (55.6%), diarrhea/hypertension (33.3%)	[114]
Sorafenib	Phase III clinical trials	RAIR-TC	Median PFS[c]	HFSR: 76.3%, diarrhea: 68.6%	[115]
Apatinib	Phase III clinical trials	RAIR-TC	Median PFS	Hypertension: 34.8%, HFSR: 17.4%	[116]
Donafenib	Phase II clinical trials	RAIR-TC	Median PFS	Hypertension: 22.8%	[117]
Lenvatinib	Phase III clinical trials	RAIR-TC	Median PFS, RR[d]	Hypertension: 67.8%, diarrhea: 59.4%	[118]
Lenvatinib	Prospective study	RAIR-TC	1 year (OS, TTF, TFS, PFS)[e]	Hypertension: 61.4%, HFSR[g]: 10.2%	[119]
Cabozantinib	Phase III clinical trials	RAIR-TC	Ongoing	Ongoing	[120]
Axitinib	–	RAIR-DTC, MTC	Median PFS, ORR[f]	Fatigue: 53.2%, diarrhea: 36.2%	[121]
Axitinib	Phase II clinical trials	RAIR-TC	Median PFS, ORR	Hypertension: 12%	[122]
Vemurafenib	Phase II clinical trials	BRAFV600E (+) [h]RAIR-TC	Median time to follow-up	Lymphopenia: 8%	[123]
Pazopanib	Phase II clinical prospective study	RAIR-TC	PR	Thromboembolism: 1.7%	[124]
Regorafenib	Case report	RAIR-FTC	Persistent reaction	–	[125]

[a]Partial response rate

[b]Thyroid gland globulin

[c]Median progression-free survival

[d]Response rate

[e]1 year (Overall survival, Treatment failure rate, Treatment-free survival, Progression-free survival)

[f]Objective response rate

[g]Hand-foot skin reaction

[h]BRAF V600E mutation

the therapeutic potential of other kinase inhibitors for RAIR-DTC. Notably, the efficacy of some drugs still needs to be assessed by prospective studies (Table 1).

Kinase inhibitor resistance

Although kinase inhibitors can provide some efficacy in patients with RAIR-DTC, the development of resistance to kinase inhibitors during treatment will limit the use of these drugs. For example, the expression levels of miR-124-3p and miR-506-3p (miR-124/506) were significantly decreased in TC cells of patients not sensitive to sorafenib treatment. Enhancer of zeste homolog 2 (EZH2) directly inhibited the expression of miR-124/506. Inhibition of E2H2 restored the sensitivity of cancer cells to sorafenib [126]. KRAS G12S mutation can promote the progression of papillary thyroid cancer. Both BRAFV600E and KRAS are in the RAS/RAF/MEK/ERK pathway in somatic cells, so their mutations are mutually exclusive. Acquired KRAS G12V in TC patients with BRAF V600E mutations after treatment with BRAF/MEK inhibitors (dabrafenib and trametinib) may be one of the reasons for the emergence of resistance to this treatment regimen [127]. Clinical Ref-1 expression is associated with BRAF mutation and poor prognosis in PTC. An increased intrinsic level of Ref-1 reduces the sensitivity of BRAFV600E PTC to vemurafenib. Treatment with Ref-1 inhibitors such as E3330 combined with vemurafenib can significantly inhibit cell growth and overcome drug resistance caused by vemurafenib alone [128]. IGF2BP2 binds to the N6-methyladenosine binding site in the ERBB2 mRNA coding sequence, which can increase the expression of ERBB2 mRNA, thereby causing selumetinib resistance of RAIR-DTC [129]. BRAF/CRAF dimerization was found to be a potential resistance mechanism to vemurafenib. The pan-Raf inhibitor LY3009120 successfully overcame vemurafenib resistance and inhibited the growth of DTC cells in vitro and in vivo. The combination of obatoclax and LY3009120 provides a basis for the treatment of RAIR-DTC [130].

Kinase inhibitors in combination with immunotherapy

Tumor immunotherapy has made some progress in cancer treatment. The development of tumor immunotherapy mainly tends to involve immune checkpoint blockade (ICB) therapy. At present, cytotoxic T-lymphocyte antigen 4 (CTLA4), PD1 and PDL1/PDL2 have been found. The PD-L1/L2-PD-1 interaction occurs mainly in the periphery. The combination of CTLA-4 and PD-1 has potential synergistic effects [131]. A high level of MDSCs is associated with a poor response. Jena et al. reviewed the principle, current progress and treatment prospects of immunotherapy for advanced thyroid cancer in detail [132]. Studies have shown that BRAFV600E can promote the development of thyroid cancer by increasing the penetrance of MDSCs. The former can reactivate TBX3 (T-box transcription factor 3, which is involved in the initiation and progression of cancer) and upregulate CXCR2 ligand in a TLR2/NF κB-dependent manner, leading to MDSCs recruitment into the tumor microenvironment. Therefore, inhibition of CXCR2 or MDSCs can improve the therapeutic effect of MAPK inhibitors [133]. Another study found that lenvatinib monotherapy increased tumor-infiltrating macrophages, CD8 + T cells, regulatory T cells, and especially polymorphonuclear myeloid suppressor cells (PMN-MDSCs), but in an orthotopic mouse ATC model, lenvatinib combined with a checkpoint inhibitor targeting the programmed cell death pathway. The combination of lenvatinib and anti-PD-1 can reduce the expansion of PMN-MDSCs. The combination of lenvatinib and anti-GR-1 antibody can improve the expansion of PMN-MDSCs caused by lenvatinib monotherapy and improve the antitumor effect of lenvatinib. These results suggest a promising combination of immunotherapy and multienzyme inhibitors [134]. Therefore, whether combination therapy with kinase inhibitors or combination therapy with kinase inhibitors and immunotherapy can solve the limitations of the above kinase inhibitors is still a problem that needs to be further explored. Some research into drug combinations is continuing (Table 2).

Kinase inhibitors in combination with autophagy inhibitors

Since autophagy is involved in the pathogenesis of RAIR-DTC to some extent, combining autophagy with kinase inhibitors may be a new way to treat RAIR-DTC (Table 3), but the study of the combined treatment is still in the preclinical research stage. Further clinical research is needed to confirm the feasibility of this method. Moreover, clinical studies have been carried out or are being carried out for other cancer types, and studies on RAIR—DTC are still needed to further verify the effectiveness and feasibility of this method. The current research on treatment may provide new research ideas and directions for future research on RAIR-DTC.

Gene therapy for RAIR-DTC

MSC-based gene delivery methods are useful for the treatment of neurological diseases [158]. One study found that NIS radioactive iodine gene therapy can regulate the phenotype of cancer cells and enhance the killing function of CTL in mouse tumor models, which is of great significance for the combination of hNIS and immunotherapy in cancer patients who have failed conventional therapy and are at risk of recurrence [159]. In addition, wild-type NIS DNA codons were replaced with new codons, which are most commonly used in human gene translation, to optimize the NIS gene coding sequence, and vectors composed of wild-type NIS

Table 2 Different combination treatment regimens

Drug	Clinical-trial number	Cancer	Patients	Cite
Vemurafenib + CDX-3379	NCT02456701	BRAF (+)[a] RAIR-TC	6	[135]
Atezolizumab + Vemurafenib + Cabozantinib	NCT03625141	Melanoma with central nervous system metastases	80	[136]
Camrelizumab + Apatinib	Case report	RAIR-TC	1	[137]
Lenvatinib + Pembrolizumab	NCT02973997	RAIR-TC	30	[138]
Tucatinib + Trastuzumab + Pertuzumab	NCT05132582	HER2 (+)[b] metastatic breast cancer	Ongoing	[139]
Encorafenib + Binimetinib	NCT01909453	BRAF (+) melanoma	577	[140]
Dabrafenib + Trametinib	NCT01723202	BRAF (+) RAIR-DTC	53	[141]
Sorafenib + Everolimus	NCT02143726	RAIR-HTC	34	[142]
Dabrafenib + Trametinib + Lapatinib	–	BRAF (+) PTC	–	[143]
Pasireotide-LAR + Everolimus	–	RAIR-DTC, MTC	42	[144]

[a]BRAF mutation

[b]HER mutation

Table 3 Combined treatment model of autophagy and kinase inhibitors

Drug	Cancer	Research	Cite
Sorafenib + CQ[i]	TC	In vitro + in vivo	[145]
Apatinib + HCQ[j]	PTC	In vitro + in vivo	[146]
Selumetinib + Autophagy inhibitors	CC[a]	In vitro	[147]
Dabrafenib + Trametinib + HCQ	Melanoma	Phase I/II clinical study	[148]
Trametinib + HCQ/Cobimetinib + HCQ	KRAS (+)[b] PDAC	–	[149]
Gefitinib + Curcumin	NSCLC[c]	In vitro + in vivo	[150]
Lenvatinib + HCQ	HCC[d]	In vitro + in vivo	[151]
Dabrafenib/Selumetinib + Panobinosta	BRAF (+)[e] PTC	In vitro	[152]
Apatinib + CQ	CRC[f]	In vitro + in vivo	[153]
Apatinib	NSCLC	In vitro + in vivo	[154]
Binimetinib + HCQ	Metastatic PDAC[g]	Phase two clinical trials	[155]
Cobimetinib + Atezolizumab + HCQ	KRAS (+) AC	Phase I/II clinical study	[156]
Trametinib + ONC212	PDAC[h]	In vitro	[157]

[a]Colon cancer
[b]KRAS mutation
[c]Non-small cell lung cancer
[d]Hepatocellular carcinoma
[e]BRAF mutation
[f]Colorectal cancer
[g]Pancreatic ductal adenocarcinoma
[h]C: adenocarcinoma
[i]Chloroquine
[j]Hydroxychloroquin

and optimized NIS (opt-NIS) were introduced into thyroid and cervical cell lines, respectively. This study found that compared with wild-type NIS, opt-NIS could increase NIS protein synthesis at the genetic level, enhance RAI uptake by cells, effectively reduce tumors, and prolong the survival of tumor-bearing mice [160]. It is important to note that if this method of treatment needs to address the following questions, what method of gene delivery is reliable? How can we determine that opt-NIS is correctly delivered to the target site and functions normally? How to address the potential toxicity and immune activation associated with this type of therapy? For gene therapy, long-term tracking of gene expression is very important. Tracking of gene therapy can be achieved through reporter genes because reporter gene imaging (RGI) can determine the biological distribution, extent and persistence of viral gene expression and/or viral infection. The most commonly used reporter gene in humans is NIS, which is delivered by viruses to accurately track viral infection and tumor spread, and to track tumor response to treatment. However, the use of this method needs to address endogenous NIS interference, efflux of radioactive tracers by NIS expressing cells, and low transduction/expression of NIS transgenes in transduction target tissues [161]. Regarding endogenous NIS interference, studies have found that the combination of minke whale NIS and perchlorate can block endogenous NIS transport activity, and to some extent solve the problem of endogenous NIS interference [162]. Gene therapy has therapeutic potential for RAIR-DTC. If the above problems can be solved, this method will have a positive therapeutic effect on patients. ALK fusion, usually STRN-ALK, has a higher incidence than DTC in human poorly differentiated thyroid cancer, and progression of DTC to PDTC is associated with loss of iodine affinity and adverse outcomes in progressive dedifferentiation. Preclinical studies have demonstrated that well-differentiated thyroid cancer (PTC) ($n=26$), PDTC ($n=21$), and ATC ($n=8$) often co-exist in the same thyroid gland in transgenic mice with thyroid-specific expression of STRN-ALK and double-allelic deletion of p53. PDTC type 1 (PDTC1) and PDTC2 (PDTC2), the latter of which has higher thyroid differentiation genes (e.g., NIS). These findings may explain why some patients can take RAI in initial treatment but no longer take RAI in subsequent treatment. ALK fusion drives DTC dedifferentiation. Current studies have confirmed that NIS downregulation induced by ALK fusion is a prerequisite for RAI refractory, which can lead to increased signal transduction output of MAPK, JAK/STAT3 and PI3K/AKT/mTOR. Significant Alk-dependent downregulation associated with most thyroid differentiation and iodine-metabolizing/transporter genes, including NIS, Duox1/2, and Tg, can be reversed by corresponding inhibitors. On the one hand, ALK can be

reversed by its inhibitors, such as crizotinib and ceritinib. On the other hand, can gene therapy targeting the fusion gene be possible [163, 164]?

Astatine therapy for RAIR-DTC

Astatine, an alpha particle transmitter, has similar chemical properties to iodine, but it can emit alpha particles with higher linear energy transfer (LET). Studies have found that adding ascorbic acid can increase the radiochemical purity of 211At. If 211At can be proved to be more beneficial to RAIR-DTC, it is necessary for DTC patients with disease progression to be targeted with more effective radionuclide. In addition, the evaluation of the side effects of the drug will contribute to the clinical application of 211At [165]. Watabe and Tadashi et al. compared the efficacy of astatine and iodine in a mouse model of TC and found that astatine may have broad clinical application prospects in the treatment of advanced DTC [166]. In addition, the authors initiated clinical trials of astatine against RAIR-DTC, aiming to obtain approval of targeted α-therapeutic agents [167].

Other therapies of RAIR-DTC

Therapeutic potential of pyruvate carboxylase

Study has confirmed that PTC has a very active tricarboxylic acid cycle, in which pyruvate carboxylase (PC) plays a key role [168]. For RAIR-DTC, PC can not only promote cell proliferation, invasion and metastasis, but also inhibit the expression of TSHR, NIS, TPO and TG genes. In addition, PC can also activate MAPK pathway and inhibit the iodine uptake capacity of cells. The above effect can be inhibited by PC inhibitor ZY-444. Therefore, pyruvate carboxylase may be a potential therapeutic target. PRDM16 is a member of the zinc finger family in the PR domain. Liu et al. demonstrated that PRDM16 can directly bind to the PC promoter and inhibit its expression at the transcriptional level in PTC tissues. PRDM16 is usually down-regulated in TC tissues, and this molecule is a potential molecular target for RAIR-DTC treatment [169, 170].

Rutin therapy for RAIR-DTC

Rutin is a glycoside form of quercetin. Goncalves et al. demonstrated for the first time that rutin can increase endogenous NIS expression and iodide uptake, and it is an adjunctive drug with important potential for radioiodine therapy [171]. Goncalves, C.F et al. discussed the specific mechanism of rutin promoting iodine uptake. They found that rutin could increase the mRNA and protein expression of NIS in PCCL3 and reduce RAI efflux. In addition, rutin could regulate the subcellular localization of NIS and promote the increase of NIS membrane localization. As an effective scavher of ROS, rutin could significantly reduce the intracellular ROS concentration and inhibit AMPK action [172].

Nevirapine therapy for RAIR-DTC

Nevirapine, a non-nucleoside reverse transcriptase inhibitor, was originally developed to treat HIV. Nevirapine was found to have a potential role in the treatment of RAIR-DTC. In dedifferentiated thyroid cancer, Nevirapine can significantly increase the expression of thyroid-related genes, TSHR, NIS, TPO, and PAX8. On the one hand, the expression contents of NIS mRNA and TSH mRNA increase accordingly. On the other hand, Increase NIS-mediated radio-iodide uptake by dedifferentiating the TSHR/CAMP/CREB/PAX8 pathway in thyroid cancer cells. For RAIR-DTC with decreased NIS expression, Nevirapine can upregulate NIS expression in a time-dependent manner from the aspect of gene expression. Although the expression increases both in cytoplasm and cells, the latter increases significantly, ultimately leading to increased uptake of RAI by RAIR-DTC [173]. Unfortunately, there are few clinical studies on the treatment of RAIR-DTC by Nevirapine at present, and the potential effect of Nevirapine in the treatment of RAIR-DTC still needs a large number of clinical trials to provide evidence-based evidence.

Therapeutic potential of estrogen-related receptors

A latest study has found that ERRγ inverse agonist GSK5182 enhances NIS protein function by regulating ERRγ and MAP kinase signaling, thereby increasing the response of RAIR-DTC cells to radioactive iodine [174].

Discussion

Further study of the molecular mechanism of RAIR-DTC is beneficial to find potential therapeutic targets. Based on the above discussion on the pathogenesis of RAIR-DTC, The occurrence of iodine resistance may be a result of many factors interact. For example, In the process of abnormal degradation of NIS, TME conditions such as hypoxia and nutrient deficiency, BRAFV600E gene mutation, epigenetic processes such as histone deacetylation usually play a role as inducing factors in iodine resistance, reactive oxygen species, and the expression of histone deacetylation. The energy sensor AMPK, the nutrient sensor mTORC1, ROS and the endoplasmic reticulum stress process usually function as the molecular interaction center of iodine

resistance, while the autophagy pathway usually acts as the integrated effector hub of iodine resistance, which ultimately leads to the degradation of NIS. If we can effectively assess the growth environment of cancer cells and systematically elucidate the pathogenesis of RAIR-DTC, we can provide more personalized treatment for different RAIR-DTC patients.

The targeted therapy of advanced RAIR-DTC mainly uses kinase inhibitors. Currently, the approved drugs include sorafenib, lenvatinib, cabozantinib [104, 105, 109]. However, on the one hand, patients with long-term single drug use will have adverse reactions such as hypertension and hand-foot syndrome [115, 119], and on the other hand, drug resistance will occur. Some studies have shown the causes of drug resistance to targeted drugs, such as the reactivation of a signaling pathway [127], which provides a strong basis for drug resistance therapy. However, many drug resistance mechanisms are still being explored, notably, the interaction between the pathogenic factors of RAIR-DTC may lead to the insensitivity of patients to some targeted drugs [128, 130]. High rates of adverse reactions and drug resistance may limit the use of kinase inhibitors to some extent, but several studies have evaluated combination therapy options, currently approved treatment regiments indicate that BRAF inhibitors combined with MEK inhibitors are promising for the treatment of BRAF mutant DTC [27]. Jafri et al. discussed the therapeutic prospect of combined BRAF/MEK inhibitors for patients with RAIR-DTC metastatic TC on the basis of previous studies, but did not show whether the combined treatment could improve the progression-free survival or overall survival of the patients. Results of multi-center randomized controlled trials are still needed to supplement the treatment results of these drugs [26]. Another study showed that the efficacy of two-drug combination therapy in BRAF mutation DTC patients was not significant compared to that of single drug therapy [66]. In addition, on the one hand, cell protective autophagy is associated with reduced drug efficacy, for example vemurafenib induces protective autophagy in the treatment of PTC with BRAFV600E gene mutation, which reduces the efficacy of Vemurafenib [62]. Therefore, combined treatment with autophagy inhibitors can further improve the efficacy of vemurafenib. Excessive ROS is directly related to protective autophagy, Studies have confirmed that porous cerium dioxide nanorods (PN-CeO2) can catalyze ROS clearance and inhibit protective autophagy in breast cancer, lung cancer and other cells [175]. Based on the above discussion on the pathogenesis of RARI-DTC, it can be found that ROS plays an intermediate hub role. On the one hand, ROS can activate autophagy in RARI-DTC to a certain extent; on the other hand, ROS can regulate NIS transcription level, NIS cell membrane localization and NIS activity, and ultimately cause the reduction of NIS content in TC cell membrane. The above PN-CeO2 has a good clear ROS effect, but its effect has not been verified in RARI-DTC. If its effect in RARI-DTC can be verified in the future, it will provide the basis for preclinical research for the application of PN-CeO2 alone or PN-CeO2 combined with vemurafenib in the treatment of RAIR-DTC. On the other hand, autophagy is associated with NIS degradation, in RAIR-DTC where autophagy activation affects NIS degradation, the combination of autophagy inhibitors will help improve the efficacy of other drugs. Vanadium pentoxide nanoparticles (VnNp) are a kind of reactive oxygen species that can selectively induce the death of breast cancer cells. These particles change the antioxidant system of cells and accumulate in lysosomes and mitochondria, leading to damage to lysosome and mitochondrial function. Long-term effects of VnNp can lead to cell cycle arrest, inhibit cell migration and enhance the occurrence of apoptosis [176]. Starvation therapy is one of the methods of cancer treatment. Wang et al. found that GO-Alg@CaP/CO (a novel nanomodulator) could promote the treatment of cancer dominated by nutrient deficiency by enhancing mitochondrial Ca2 + overload and obatoclax-mediated inhibition of autophagy by curcumin [177]. In addition, it was the first study to show that natural flavonoids can affect 125 iodine content in human NIS stable transfected follicle cell line FTC133. Although most flavonoids can reduce 125 iodine content in FTC133, myricetin can increase 125 iodine content and reduce effluence, resulting in increased iodine content in FTC133 cell line [178]. In recent years, studies on the mechanism of rutin promoting iodine uptake have continued to deepen. Existing studies have confirmed that rutin can not only promote the expression of NIS, but also promote the distribution of NIS to the PM, but also effectively clear the intracellular ROS concentration and inhibit AMPK [172]. Rutin has certain potential to assist 131 iodine therapy. If subsequent clinical trials can further prove that rutin has a positive effect on RAIR-DTC patients, then strong clinical evidence will be provided for the application of such drugs. Combined with the specific pathogenesis of RAIR-DTC, the above methods can provide a new potential direction for its treatment.

Effective prevention of disease progression is more significant than subsequent active treatment. For iodine-refractory thyroid cancer, if the prognosis can be determined effectively before disease progression or after initial iodine treatment, it will provide positive guidance for the follow-up treatment of these patients. Manohar et al. found in a retrospective study that 18F-FDG PET/CT metabolic parameters were helpful in determining the volume and biological variation of metastatic tumor load. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) can be used for dynamic risk stratification of PFS and complement Tg-DT in metastatic RAI-R DTC patients

to predict prognosis in clinical course. Another study reconfirmed the useful guiding role of 18F-FDG PET/CT in the clinical management of RAI-R-DTC and avoided further unnecessary RAIT. In addition, 177 Ga-PSMA PET/CT imaging appears to be helpful in detecting lesions not detected by FDG PET/CT and in evaluating the response of RAI refractory DTC patients to treatment with 617Lu-PSMA-68. In addition, the independent predictors APOBEC SBS13 and TERTp were highly predictive of RAI impermissibility in patients with PTC when mutated alone, but when combined, they significantly increased the likelihood of predicting RAI impermissibility in PTC. If mutations of these molecules were known in advance of treatment. The adjustment of follow-up treatment plan will have positive significance [107, 179, 180].

The treatment of advanced RAIR-DTC is an urgent problem. Fortunately, researchers are constantly exploring new therapeutic targets, discovering new targeted agents, evaluating the efficacy of different combinations of therapies, and trying to find out the exact methods for determining the prognosis of RAIR-DTC, although some are still in the basic stage of research. But with follow-up studies and clinical trials, it could 1 day benefit patients.

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval This article is a review, and what we do is to summarize the data and materials of published articles and put forward our opinions. This work involves both human subjects and specimens collected from patients, and does not involve any animal experiments.

Informed consent This paper is a review. What we have done is to summarize the data of published articles and put forward our opinions, which does not involve human study participants and their informed consent. The chart content of this paper is a summary of published articles, which does not involve the privacy and informed consent of human participants.

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