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MINI-REVIEW

The sodium iodide symporter (NIS) as theranostic gene: potential role in pre-clinical therapy of extra-thyroidal malignancies

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Abstract

Purpose Sodium iodide symporter (NIS), as a broadly exploited cancer theranostic molecule, has attracted considerable interest in non-thyroidal tumors. Several groups have investigated the significant potential of the NIS gene to induce radioiodine accumulation across various tumor types. In this review, we discuss the role of NIS as a theranostic gene in pre-clinical extra-thyroidal cancer therapy and highlight the remarkable progress in the viral and non-viral transgene transfer systems including oncolytic viruses, engineered mesenchymal stem cells (MSCs) and synthetic polyplexes.

Methods A literature search was conducted using PubMed, Scopus, and Google Scholar databases. In addition, the keywords "sodium iodide symporter", "gene transfer", "extra-thyroidal malignancies", "viral transfer system", "non-viral transfer system", and "^{131}I" were used.

Results Following the exclusion of letters, editorials, commentaries, and duplicate publications, this review summarized preclinical studies that used viral and nonviral NIS delivery methods in conjunction with ^{131}I to describe the effective role of combination therapy.

Conclusion NIS-mediated expression in combination with ^{131}I can be considered a promising approach in the preclinical treatment of extra-thyroidal malignancies and metastases. Malignant cells expressing NIS are thought to accumulate radionuclides intracellularly, which contributes to the remarkable therapeutic effects observed.

Keywords Sodium Iodide symporter · ^{131}I · Gene transfer · Viral transfer system · Non-viral transfer system · Extra-thyroidal malignancies

Abbreviations

PET	Positron emission tomography
NIS	Sodium iodide symporter
hNIS	Human sodium iodide symporter
BCL2	B-cell lymphoma 2
MCF -7	Michigan cancer foundation-7
PI3K	Phosphoinositide 3-kinases
IO^-	Hypoiodite
at-RA	All-trans retinoic acid
$^{99m}TcO_4^-$	99MTc pertechnetate
^{123}I	Iodine-123
Tc	Thyroid cancer
IHC	Immunohistochemistry
IFNβ	Interferon beta (IFNβ)
MV	Measles viruses
PLLA	Poly-L-lactic acid
SMAD	Small mothers against decapentaplegic
DSBs	Double-strand breaks
KCNQ1	Potassium voltage-gated channel subfamily Q member 1
KCNH2	Potassium voltage-gated channel subfamily H member 2
LARG	Leukaemia-associated RhoA-guanine exchange factor
SPECT	Single photon emission computed tomography
^{131}I	Iodine-131

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^{188} Re	Rhenium-188
HDACi	Histone deacetylase inhibitor
TSH	Thyroid stimulating hormone
MEK	Mitogen-activated protein kinase
CT	Computerized tomography
ATP	Adenosine triphosphate
At-211	Astatine-211
^{124}I	Iodine-124
TAAs	Tumor-associated antigens
TERT	Telomerase reverse transcriptase
VSV	Vesicular stomatitis virus
LPEI	Linear polyethylenimine
HuH	Human hepatocellular carcinoma
AuNCs	Ultrasmall gold nanoclusters
PEG	Polyethylene glycol

Introduction

The sodium iodide symporter (NIS), a transmembrane glycoprotein on the basolateral membrane of thyroid cells that actively participates in sodium and ion co-transports, is one of the oldest targets for the diagnostic and therapeutic application of radioiodide [1, 2]. The cloning of the NIS gene, in 1996 by Carrasco et al., has provided a powerful antitumor tool via the development of robust therapeutic application along with a sensitive reporter gene into non-thyroidal tumors [3]. NIS greatly facilitate in vivo real-time tracking performance of biological process through the use of whole-body imaging modalities such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) [4]. To date numerous viral and non-viral delivery systems including viral vectors, oncolytic viruses, engineered MSCs, and polyplexes are represented as a promising platform for facilitating gene delivery into target cells.

The NIS-expressing cells via absorbing β-emitting radioisotopes like ^{131}I and ^{188}Re induce cell death [5, 6]. The radiopharmaceutical ^{131}I, a theranostic agent emitting both 90% beta and 10% gamma particles, destroys target cells through direct and indirect mechanisms [7]. The potential destroying capability of ^{131}I in the direct route imposes through cell proliferation inhibition, increasing apoptosis by down-regulation of the BCL2 gene and inducing cell cycle arrest. Moreover, bystander or non-targeted effects is an indirect way that drives cell death via β-particulate radiation that occurs in the surrounding cells with path length penetration of 2.4 mm in tissue [8–10]. Currently, ^{131}I is mostly utilized in thyroid malfunction as the high expression of NIS on the thyroid gland. Studies have shown other tissue including the mammary gland, the choroid plexus, the salivary gland, and stomach parietal cells expressing significant levels of NIS that can be used as a therapeutic target [11]. In this context, one of the early efforts was conducted by Spitzweg et al. who showed that prostate cancer cells expressing NIS induce cell death in androgen-sensitive human prostate adenocarcinomas after administration of ^{131}I [12]. Further, another study found that the NIS protein plays a role in the accumulation of ions in breast cancer metastatic sites [13]. As a result, evaluating ^{131}I for the treatment of other cancers has become more critical.

In this review, molecular events involved in the NIS-mediated treatment of extra-thyroidal malignancies, NIS regulatory mechanisms, and preclinical studies conducted in this field will be discussed. In addition, novel strategies like combinatorial therapeutic approaches to improve the efficiency of NIS-mediated iodine therapy in extra-thyroidal malignancies will be evaluated.

NIS functional characterization and regulation

The human NIS (hNIS) gene, localized on chromosome 19p12–13.2 and containing 1929 nucleotides comprising 15 exons and 14 introns, encodes a 643-amino acid protein with 13 transmembranes helix and molecular weight approximately 90–100 kDa. Several sorting motifs actively participate in the regulation of NIS localization, but the underlying molecular mechanisms remain poorly understood [2]. Moreover, post-translational modifications, including phosphorylation, glycosylation, and ubiquitination, have critically affected NIS interactions, localization, and activity. Studies have demonstrated three crucial N-linked glycosylation sites in the NIS protein structure lead to maturation and acquisition of appropriate weight for the NIS migration. A survey by Levy et al. showed NIS glycosylation has a critical role in protein stabilization and folding and does not require correct targeting of the protein on the plasma membrane. In addition, western blot analysis revealed the migration of NIS protein (at lower molecular weight) in other tissues was affected due to incomplete glycosylation [14].

NIS protein regulates by both transcriptional (epigenetic) and post-translational mechanisms (subcellular localization) [6]. Depending on the species and tissue context, different regulatory elements act on the NIS gene with varying degrees of enhancer and promoter activities to modulate the transcription of NIS. In addition, NIS gene is regulated by three major epigenetic mechanisms, including DNA methylation, histone modification, and nucleosome positioning [15]. For example, histone deacetylase inhibitors (HDACi), which are known to exert epigenetic control by affecting non-histone proteins such as transcription factors and molecular chaperones, regulate chromatin structure and gene expression. In this context, Rathod et al. have well demonstrated that the use of bHDACi together with ^{131}I

significantly increases the expression of NIS and reduces the survival of MCF-7 cells (Fig. 1) [16].

TSH and iodide are two essential factors that control NIS expression and localization under physiological conditions [17, 18]. In addition, thyroglobulin, protein–protein interactions, through potassium voltage-gated channel subfamily Q member 1 and potassium voltage-gated channel subfamily H member 2 (KCNQ1–KCNH2) K^+ channel are other mechanisms that are involved in the NIS regulation [4]. Several studies have confirmed intracellular expression of NIS in the thyroid and breast cancerous tissues [19]. In a study Peyrottes et al. showed that the expression level of NIS in thyroid and breast cancer is low and intracellular tracking was correlated with non-specific signals. These discouraging results allowed scientists to focus on NIS post-translational regulation to increase the uptake of iodide in tumor cells [20]. In addition, signaling pathways are shown to interfere with the expression and regulation of NIS in human cancers. In this regard, Knostman and colleagues revealed activation of PI3K significantly increases the expression of NIS in the MCF-7 cell line [21]. Furthermore, the MEK signaling pathway regulates NIS expression in thyroidal and breast tissue. Recently, Zhang et al. demonstrated MEK inhibition linked to NIS lysosomal degradation [22]. Also, the role of the MEK signaling pathway is highlighted in breast cancer via NIS protein stability and oncogenic transformation.

NIS expression in extra-thyroidal and therapeutic applications

As an essential iodide transporter for the biosynthesis of thyroid hormone, NIS protein is distributed in some extra-thyroidal organs, including salivary glands, renal tubules, the stomach, the lactating breast, etc. Studies have found that the NIS expression, regulation, function, subcellular localization, and glycosylation at extra-thyroidal organs depend on individual tissues and I^- requirement/content [23].

In many cases, NIS is involved in multiple functions, including: (1) recycling and retaining as much I^- as possible, either from food, recycling of secondary metabolism, or reabsorption from urine, thereby releasing I^- into the blood and reaching the thyroid gland; (2) supply the fetus and the newborn with I^- and (3) provides I^-, which exerts an antioxidant role by reducing the levels of ROS, and finally ensure that I^- exerts a potent antiviral and antimicrobial protective function when converting to hypoiodite (IO^-) [23]. In addition, several advantages have been reported for the use of NIS compared with other reporter genes, including the human origin of NIS, no need for prior radiolabeling, which reduces the corresponding costs, the possibility of using different imaging systems such as PET, SPECT, combination of SPECT or PET with computerized tomography (CT) to provide anatomical information about cells expressing

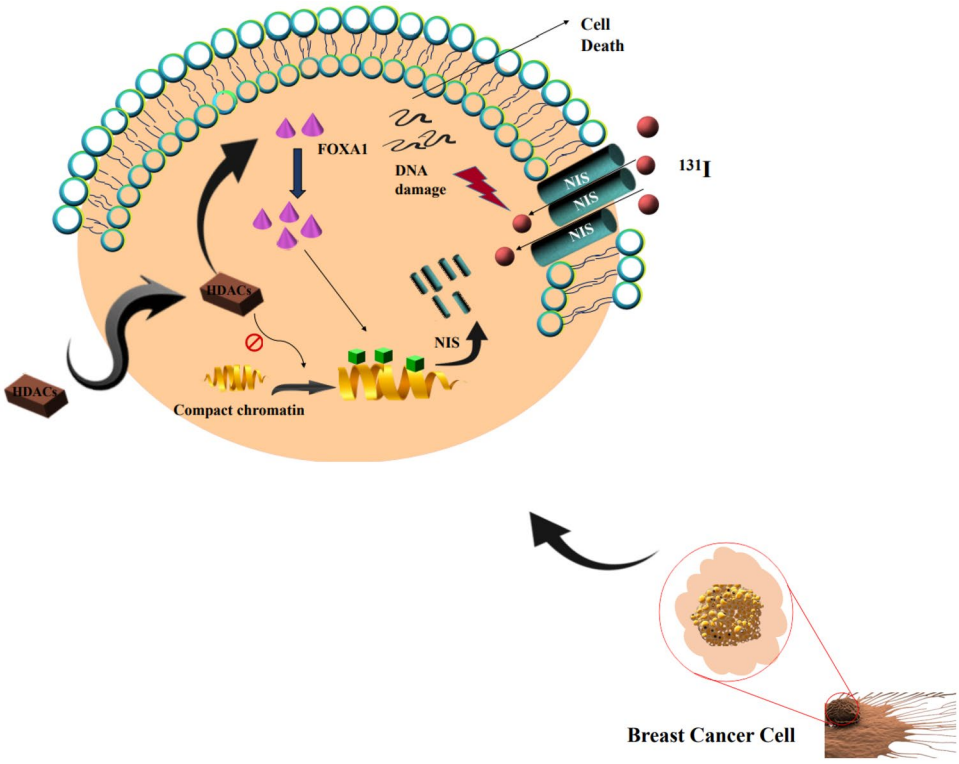

Fig. 1 Molecular basis of breast tissue-specific transcriptional modulation of NIS. Pretreatment with a histone deacetylase (HDAC) inhibitor enhances endogenous expression of NIS, which is effective for ^{131}I therapy in breast cancer models

NIS, and improvement of detection sensitivity due to signal amplification by the accumulation of intracellular substrate.

As mentioned previously, the NIS protein is expressed in the normal breast tissues during pregnancy and lactation. Studies have shown treatment of nonlactating mice with oxytocin alone, consequently increased levels of NIS expression and accumulation of radioiodide [19]. Interestingly, tumor expression of NIS has been detected in animal models of breast cancer as well as in human samples. Analysis of human breast cancer by Tazebay et al. well-showed the NIS was expressed at more than 80% of samples when compared with normal nonlactating breast tissue [19]. Imaging studies with various substrates have opened an exciting chapter in the use of NIS as a theranostic tool in endogenous NIS-expressing tumors [13]. In contrast, NIS is not always localized on the surface of the cell membrane, which may explain the discrepancy between those breast tumors expressing NIS and those absorbing radioiodide. Therefore, comprehensive clinical trials are needed to characterize the results of radioiodide therapy in metastatic breast cancer.

However, a recent study in cancer and metastasis has confirmed the oncogenic effects of intracellularly retained NIS via its interaction with leukaemia-associated RhoA-guanine exchange factor (LARG) through the PI3K/AKT/mTOR pathway. This metastatic property could recruit intracellular NIS toward the plasma membrane, making tumors amenable to ^{131}I radiotherapy, which has the additional beneficial effect of slowing tumor progression [48, 49].

The results of in vitro experiments illustrated that all-trans retinoic acid (atRA) alone or in combination with hydrocortisone, adenosine triphosphate (ATP), or dexamethasone triggered the expression of NIS in the MCF-7 cell line. Furthermore, in vivo experiments confirmed that atRA significantly increased radioiodide accumulation in NIS-mediated pathways compared to controls [6, 50–54]. In addition to the expression of endogenous NIS, experimental observations have also confirmed that transferring the hNIS gene to non-thyroid tumor cells would induce iodide accumulation. These results propose that exogenous hNIS expression in tissues of interest may play an essential role in noninvasive real-time molecular imaging using the intracellular accumulation of gamma-emitting radioisotopes such as (^{123}I, ^{124}I, ^{125}I, and ^{131}I), ^{99m}TcO4-, ^{188}Re, and ^{211}At at site-specific gene expression.

One of the limitations of serial hNIS imaging is the likelihood that the radiotracer will be taken up by both malignant and normal tissue, as the hNIS protein is widely distributed in normal tissue, which may result in decreased accumulation of the radiotracer in the target structures of interest. Furthermore, the unfavorable biodistribution and accumulation of iodide in the thyroid gland is another disadvantage that must be considered. In treating extrathyroidal cancers, administration of THs to lower TSH levels is helpful to protect the thyroid gland from unwanted radiation. This strategy can be used both in treating cancers that endogenously express NIS (e.g., breast cancer) and in treating cancers induced to express NIS by gene transfer exogenously [55]. In addition, the administration of contrast media during radiological examinations is another way to notably reduce the uptake of radioiodide by NIS -transduced cells. Also, according to Dupertuis et al., potassium iodide administered 24–48 h before treatment suppressed thyroid iodide uptake after administration of a radiolabeled iodine analog [56].

Approaches to NIS gene delivery; focusing on ^{131}I combination therapies

Over the past two decades, NIS has attracted more attention in the application and optimization of gene therapy due to its dual role as a reporter and therapeutic gene. In 1997, Shimura et al., who developed a stable Tc-rNIS cell line expressing NIS, showed that subcutaneous injection of Tc-rNIS induces I^- accumulation and can be followed by the administration of ^{125}I [57]. For the first time, this study suggested that NIS can be introduced as a theranostic agent. NIS has become the counterpart for research on human cancers, which have been extensively used in cells and other organisms (Table 1). The main areas of NIS-based gene transfer are reviewed, including (a) replicative-defective viral vectors/oncolytic virus-mediated gene therapy, (b) stem cell trafficking, and (c) regenerative medicine (Fig. 2) [58].

NIS-expressing viruses approach

In cancer therapy, viral vectors are considered one of the most promising tools that allow the insertion of therapeutic genes. NIS is one of the most amazing genes because, according to the translation, it increases the accumulation of theranostic radioisotopes for imaging and therapeutic purposes.

In this context, Trujillo et al. investigated the efficacy of an hNIS-expressing adenovirus (Ad5PB_ RSV-NIS) in a prostate cancer model. Interestingly, the result showed administration of 1 mCi of ^{131}I along with Ad5PB_RSV-NIS, slowed the rates of tumor progression and increased survival through the accumulation of radioiodine into the tumor cells [34]. In addition, a study by Oneal and colleagues found that the administration of two novel conditionally replicating adenoviral vectors in combination with ^{131}I specifically induced radioisotope uptake, cytopathic effects, and viral replication in an in vitro and in vivo prostate cancer model [59].

Table 1 Recent NIS-mediated ^{131}I-therapy in pre-clinical models of cancer therapy in vivo and in vitro

Cancer type	Mechanism of action	Agent	Outcome	References
Pancreatic cancer	Vaccinia virus against PANC-1	GLV-1h153/NIS	GLV-1h153 successfully facilitated serial imaging of virotherapy using PET after combination with ^{131}I in nude mice	Haddad et al. [24]
	Measles virus (MV) against adenocarcinoma (BxPC3)	MV-NIS	NIS-mediated iodide localization caused tumor volume reduction after iodide(^{131}I) therapy	Penheiter et al. [25]
	Synthetic polymers and EGFR-specific ligand GE11 against advanced PDAC/Nonviral NIS gene delivery	LPEI-PEG-GE11/NIS	Reduction of tumor growth without significantly prolonged survival	Schmohl et al. [26]
	Tissue-specific chromogranin A promoter or viral nonspecific CMV promoter against Bon1 and QGP pancreatic tumor cells	Chromogranin A or CMV/NIS	The formation of QGP and Bon1 cell clones was prevented in vitro through the reduction of the NIS-expressing QGP and Bon1 cells after incubation with 100 µCi/ml of ^{131}I	Schipper et al. [27]
Hepatocellular carcinoma cells (HCC)	Adenoviral vector containing CMV promoter	Ad-CMV-NIS	Rapid iodide efflux in vitro/complete regression of small nodules and long-term survival in vivo	Faivre et al. [28]
	Combining focused EBRT (5 Gy) with MSC-mediated gene delivery against HuH7	EBRT/SMAD-NIS-MSCs	Prompting TGF-β-induced NIS expression by MSCs in target cells related to delay in tumor growth and prolonged survival	Schug et al. [29]
	Recombinant MSCs with HSP70B promoter	HSP70B-NIS-MSCs	Severe reduction of tumor growth and prolonged survival of animals after L-T4 pretreatment with the administration of ^{131}I and hyperthermia	Tutter et al. [5]
	Tumor-specific GTI-1.3 promoter/retroviral vector	hNIS/GTI-1.3	Transduction of this vector induces iodide transport and high radiation dose received after ^{131}I injection in hepatoma cells in vitro and in vivo	Sieger et al. [30]
	MSCs by synthetic hypoxia-responsive promoter	HIF-NIS –MSC	Reduction of tumor perfusion using ^{123}I-scintigraphy or ^{124}I-PET imaging associated with HIF to induce therapeutic effects	Müller et al. [31]
	Tumor specific AFP promoter against metastatic HCC/Adenoviral vector	AFP/NIS-pGL3	This agent induces iodide accumulation to improve the sufficient dose of ^{131}I exposure for killing a high percentage of human HepG2 cells	Willhauck et al. [32]
	EVs, as nano-sized vesicles/nonviral delivery	EV-Huh7/NIS	Induced the expression of NIS protein level associated with high cytotoxicity of ^{131}I increased DNA damage in Huh7 cells	Son et al. [33]

Table 1 (continued)

Cancer type	Mechanism of action	Agent	Outcome	References
Prostate cancer	Combination of adenovirus with RSV	Ad5PB-RSV-NIS	Accumulate circulating radioiodine into the tumor and slowing the rate of tumor growth	Trujillo et al. [34]
	Combination of adenovirus with PSMA promoter against CRPC	Ad.PSMApro-hNIS	Limited iodine accumulation in tumor tissue related to reduction of tumor volume with minimal cytotoxicity in extra tumoral tissues	Gao et al. [35]
	Probasin promoter (ARR_2PB) against androgen-dependent prostate cancer cell lines (LNCaP)	Ad-ARR_2PB/hNIS	Increasing iodide uptake in Ad-ARR_2PB/hNIS-infected LNCaP cells 3.2-fold compared with those infected with Ad-CMV/hNIS	Kakinuma et al. [36]
Breast cancer	Radiation-sensitive Egr1 promoter against TNBC/ultrasmall gold nanoclusters (usAuNCs)	BMSC-Egr1-hNIS carrying GSH@AuNCs	Inhibition of growth and volume of TNBC in vivo/successful usAuNCs internalized to tumors by an agent without destructive effects on hNIS gene performance	Zhang et al. [37]
	Non-specific targeting of cells/adenoviral infection of MSCs	MSC-NIS	Significant necrosis in cancer tissues with no adverse effects after administration of MSC-NIS along with ^{131}I	Dwyer et al. [38]
Ovarian tumors	Lentivirus-mediated E4 promoter-NIS gene therapy	BMSC-E4-NIS	Prolonged survival with no radioiodine accumulation in mice thyroid pretreated with L-thyroxine	Shi et al. [39]
Colorectal cancer cells	CEA promoter against Colorectal cancer cells (HCT 116)/adenovirus carrying the NIS/CEA	hNIS -CEA	High doses of radioiodide accumulation lead to the killing of a significant percentage of tumor cells by administration of ^{131}I	Scholz et al. [40]
	Synthetic polymers and EGFR-specific ligand GE11 against Advanced multifocal CRC liver metastases model/nonviral NIS gene delivery	LPEI-PEG-GE11/NIS	Delay in metastases spread with improved animal survival after administration of 55.5 MBq ^{131}I	Urnauer et al.(2017) [41]
	Combination of MSCs with RANTES/CCL5 promoter against Colon cancer liver metastasis	RANTES-NIS-MSC	Iodide uptake in the area of liver metastasis to reduce the progression of metastasis in vivo	Knoop et al. [42]
	Novel chimeric poxvirus (CF33) against HCT116	CF33-hNIS (orthopoxvirus Encodes a functional hNIS	The tumor-specific CF33-hNIS had high efficacy in regressing colon cancer xenografts	Warner et al. [43]

Table 1 (continued)

Cancer type	Mechanism of action	Agent	Outcome	References
Melanoma cancer cells	Telomerase-specific gene therapy against Melanoma (M14) and Colon (HT-29/adenoviral vector	hTERT or hTR/NIS	Significantly inhibited tumor growth of melanoma-derived tumor xenografts after ^{131}I, while in colon cancer-derived xenografts this result was moderate	Riesco-Eizaguirre et al. [44]
	Combination of adenovirus with tumor-specific promoter against malignant melanoma A375 cells	Ad-Sur-NIS	Significant delay in tumor growth with effective cell killing	Zhao et al. [45]
Neuroblastoma tumor (Neuro2A) cells	Synthetic polymeric vectors	CMV-NIS-pcDNA3	Significant delay of tumor growth in Neuro2A cells with no iodide uptake in non-target organs	Klutz et al. [46]
Glioblastoma tumor cells	Lipo-oligomers/tumor-specific NIS gene delivery	monoDBCO-PEG$_{24}$-GE11/NIS	A significant decrease in tumor growth correlated with monoDBCO-PEG24-GE11/NIS polyplexes induced the EGFR expression levels in the cells	Spellerberg et al. [47]

PANC-1 pancreas cancer cell-1, *BxPC3* human pancreatic cancer cell line, *EGFR* epidermal growth factor receptor, *PDAC* pancreatic ductal adenocarcinoma, *CMV* cytomegalovirus, *EBRT* external beam radiation therapy, *HSP70B* Heat shock protein 70B, *GTI-1* glucose transporter gene 1, *AFP* α-fetoprotein, *HepG2* hepatoma G2, *EVs* extracellular vesicles, *RSV* respiratory syncytial virus, *PSMA* prostate-specific membrane antigen, *CRPC* castration-resistant prostate cancer, *ARR$_2$PB* two androgen response probasin promoter, *LNCaP* Lymph node cells androgen-sensitive prostate, *TNBC* triple-negative breast cancer, *Egr1* early growth response-1, *CEA* carcinoembryonic antigen, *CRC* colorectal cancer

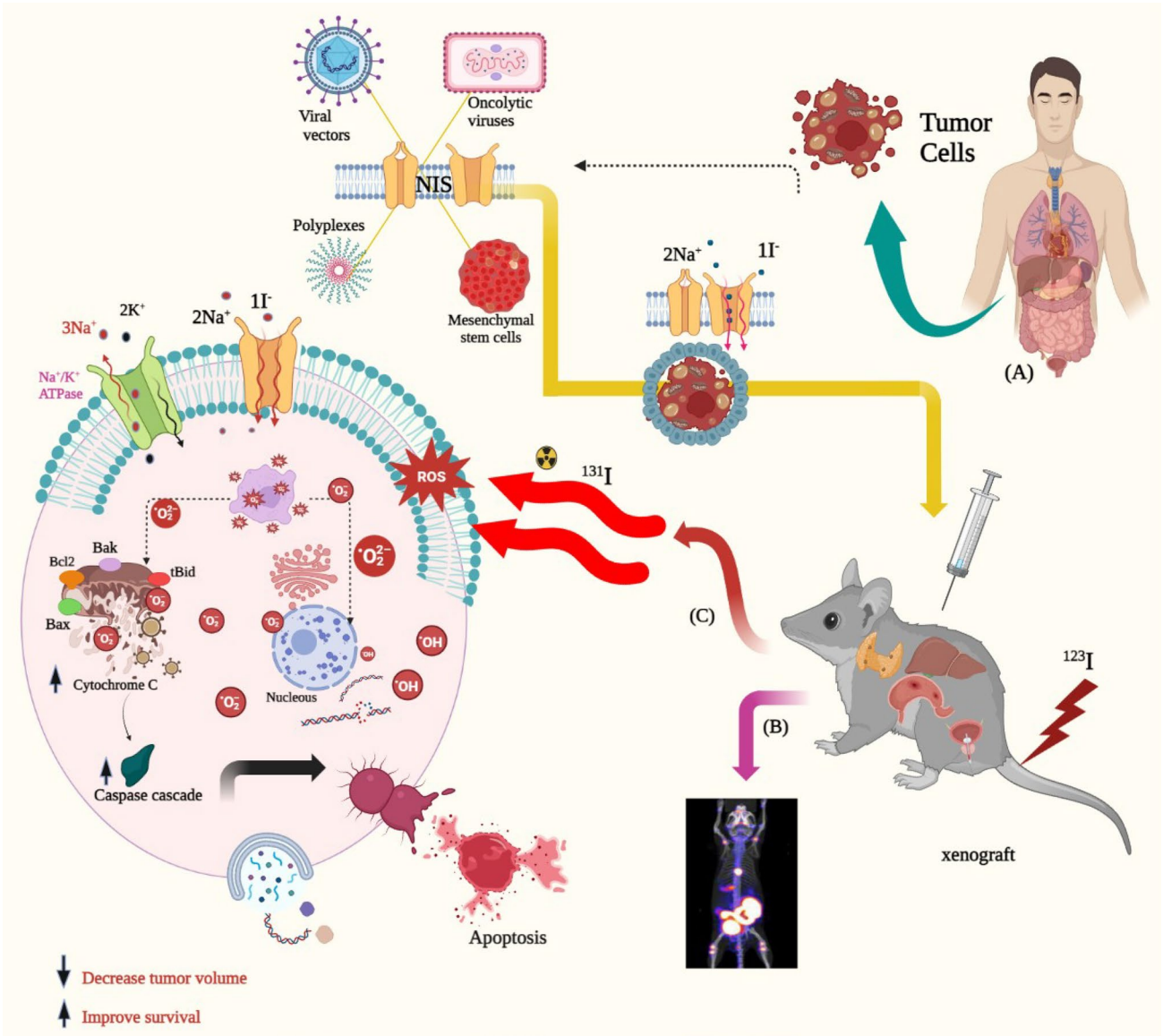

Fig. 2 Schematic representation of pathways involved in apoptosis of tumor cells treated with ^{131}I. Viral and non-viral vectors coupled with sodium iodide (Na^+/I^-) symporter increase the expression of NIS (A), and the level of NIS expression determined by SPECT—CT imaging after ^{123}I injection (B), then tumor cells are irradiated with 131-iodine, iodine irradiation causes the release of reactive oxygen species (ROS) and induces apoptosis (C)

Oncolytic viruses are another platform increasingly used in cancer therapy trials because they can preferentially infect and kill tumor cells [60]. These viruses are divided into two main groups: (1) naturally oncolytic viruses, which have an innate ability to infect and kill tumor cells like Newcastle disease virus, and (2) genetically engineered oncolytic viruses, which have been genetically engineered to replicate and destroy cancer cells such as vaccinia, Herpes simplex, adenovirus and measles virus. Oncolytic viruses typically induce antitumor responses through two distinct strategies, including direct lysis of cancer cells after induction of immunogenic cell death, the release of tumor-associated antigens (TAAs), damage-associated molecular patterns, pathogen-associated molecular patterns, and subsequently activation and recruitment of an additive immune response to the tumor microenvironment [61].

Increasing the sensitivity of tumor cells to ionizing radiation or chemotherapy, inducing immunogenic cell death, selective replication in tumor cells, and the ability to infect resistant tumor cells are some of the main advantages of oncolytic viruses. However, some issues that need to be considered in virotherapy include variability in preclinical and clinical response, limited ability to transduce tumors, and limited distribution within the solid tumor due to physical properties

[62]. Further, virus immunogenicity must also be optimized to modulate the organism's immune response to be able to replicate and spread. To address these issues, the trajectory of viral particles, the number of infected cells, and the duration and spread of viral infection must be effectively monitored [63]. Functional expression of NIS correlates with the longevity of viral replication and allows tracking of radioisotope uptake during the viral infection cycle in the tumor. After infection of the target cells, the NIS gene is translated and the protein is translocated to the plasma membrane, allowing the detection of the accumulated radiotracer. At the peak of virus replication, radiotracer absorption reaches its maximum. Finally, cell lysis releases new viral particles, causing the infection to spread and NIS to be expressed in neighboring cells.

The first experiments were performed by Peerlinck and colleagues, which demonstrated that the radiotracer accumulation was positively correlated with cell viability in mice with colorectal carcinoma. Confirmation of the results by nanoSPECT/CT and immunohistochemistry (IHC) revealed accumulation of ^{131}I in the first 48 h after infection. Thereafter, I accumulation decreased, NIS could no longer be detected at the plasma membrane, and the cells began to die [64]. In addition, the efficacy of intravenous administration of Ad5/3-hTERT-hNIS (the hTERT promoter controls an oncolytic adenovirus) in combination with ^{131}I was investigated. SPECT Analysis showed that Ad5/3-hTERT-hNIS significantly prolonged survival in a prostate cancer model compared with mock or radioiodine-only groups [65].

The remission of metastatic cancer is another critical aspect that needs to be considered in new therapies. To address this issue, systemic delivery of oncolytic viruses encoding NIS has been developed to enable imaging and treatment of metastatic lesions and detection of positive surgical margins after tumor resection [66]. Recently, Naik et al. evaluated intravenous administration of VSV-IFNβ- NIS, a novel recombinant oncolytic vesicular stomatitis virus expressing NIS and interferon β, in spontaneous canine cancer. The results showed that VSV-IFNβ- NIS is well tolerated and safe in treating advanced or metastatic disease [67]. In addition, oncolytic measles viruses expressing NIS (MV-NIS) have been successfully used as an effective theranostic modality in various cancers. Considering this perspective, Russell et al. reported an impressive response to intravenous infusion of MV-NIS for the treatment of two measles seronegative patients suffering from relapsed drug-refractory myeloma [66].

NIS gene delivery by non-viral delivery systems

A critical step in the clinical implementation of NIS gene therapy is the development and evaluation of effective, safe, and highly efficacious delivery systems not only after local but also after systemic vector application. In addition to the ability to monitor and target primary tumors, the ability to target tumor metastases is another crucial aspect to be addressed by improved targeted delivery methods. Synthetic polyplexes and mesenchymal stem cells are two promising non-viral platforms that are currently being investigated and have the potential for clinical application.

Polyplex-mediated *NIS* gene delivery

Synthetic vectors, as a promising delivery method inspired by viral biology, cover some of the current limitations of viral vectors, such as immunogenicity, difficulties in synthesis and upscaling, and limited nucleic acid transport. Recently, several generations of synthetic polycationic polymers have been investigated by Munich researchers at the LMU as delivery systems for systemic gene delivery medicine NIS [68]. Linear polyethylenimine (LPEI), a polycationic polymer, is a "gold standard" for synthetic gene delivery systems with improved targeting and higher efficiency through the incorporation of polyethylene glycol (PEG) and targeting ligands. PEG cover reduces self-aggregation by lowering the positive surface charge and provides prolonged blood circulation by evading immune recognition. Moreover, this positive surface charge has been shown to lead to high intrinsic tumor affinity. Furthermore, due to its biodegradability, no toxic side effects have been reported [69]. Up to now, several studies have evaluated tumor selectivity, biodistribution, transduction efficiency, and duration of transgene expression of these polyplexes after systemic administration using NIS-based imaging.

In a study, Urnauer and coworkers investigated the receptor specificity, transduction efficiency, and therapeutic efficacy of polymers composed of PEG and cationic amide nuclei complexed with NIS-DNA targeting sequence-defined cMET/HGFR (a dual-targeting approach) in a hepatocellular cancer model. Results showed that three cycles of polyplexes (cMBP2-PEG-Stp/NIS) and ^{131}I resulted in high tumor-selective iodide accumulation and significant tumor growth delay and prolonged survival [70]. Effective control of metastases has become an important issue in novel cancer therapy, as they are one of the main causes of disease recurrence and patient death. Liver metastases are one of the major challenges in advanced colorectal cancer, of which less than 5% are cured. Urnauer et al. designed and studied a novel polymer containing polyethylenimine, PEG, the epidermal growth factor receptor (EGFR) targeting GE11 complexed with NIS (LPEI-PEG -GE11/NIS) in liver metastases from colorectal cancer. Analysis of PET confirmed that administration of three cycles of intravenous LPEI-PEG-GE11/NIS together with 55.5 MBq ^{131}I significantly slowed

the spread of liver metastases and was associated with animal survival [41].

Nonviral MSCs- NIS gene transfer

Mesenchymal stem cells (MSCs) are a diverse subset of multipotent progenitor cells that are characterized by a panel of specific cell surface antigens and play a fundamental role in tissue regeneration [71]. The high potential of MSCs to migrate to the site of various tumor types (in vivo) makes them a useful vehicle for the targeted delivery of therapeutic agents in different cancer types. Currently, MSCs expressing NIS have emerged as a platform for the selective delivery of radionuclides for better visualization and effective treatment of metastases [72].

Dwyer et al. investigated the application of MSC-NIS along with intraperitoneal injection of ^{131}I for breast cancer imaging and therapy. Promising data support the feasibility of this approach as a novel therapy for breast cancer [38]. In addition, a study showed that mice transduced with the MSC-NIS/poly-L-lactic acid (PLLA) complex had higher iodide uptake than MSC-NIS, which was associated with the long-term survival of the mice [73].

External beam radiotherapy (EBRT) was shown to enhance the recruitment of NIS-expressing MSCs into human hepatocellular carcinoma (HuH7). Moreover, the expression of the cytokine TGFβ was strongly upregulated in HuH7 tumors after EBRT irradiation. Schug et al. investigated the combination of MSC-based NIS -mediated ^{131}I therapy under the control of a synthetic TGFB1-inducible small mothers against decapentaplegic (SMAD)-responsive promoter (SMAD-NIS-MSCs) and 5 Gy focused EBRT, resulting in growth delay up to complete tumor remission and longer survival compared with CMV-NIS-MSCs treated mice [29]. In another study, the human HSP70B promoter was selected as a candidate gene promoter for MSC-mediated NIS gene therapy (HSP70B-NIS-MSCs). The results showed that the combination of HSP70B-NIS-MSC-mediated ^{131}I with hyperthermia resulted in a significant reduction in tumor growth and prolonged survival of the animals [5].

Early growth response protein1 (Egr1) is a zinc finger transcription factor that regulates cell growth and differentiation. Egr1 expression is induced in the presence of ^{131}I. Recently, Zhang et al. constructed MSCs from bone marrow bearing both ultrasmall gold nanoclusters (AuNCs) (to improve the efficacy of radiotherapy) and hNIS under the Egr1 promoter. Based on an in vivo result, the combination of BMSC-Egr1-hNIS + AuNCs with ^{131}I reduced tumor volume by up to 56%, compared with the BMSC-Egr1-hNIS group alone (36%) [37].

Challenges and supportive strategies

Despite the suitable physical properties of α-emitting radioisotopes, it is not possible to use them routinely because of their relative unavailability. Therapeutic β-emitting radioiodide (^{131}I) is the relevant radioisotope used in studies because of its unique ability as a therapeutic agent. The effective translocation of NIS protein into the cell membrane through the induction of membrane insertion of the gene NIS leads to high performance of ^{131}I-mediated therapy for the destruction of solid tumors. Furthermore, successful iodine therapy depends on ^{131}I retention in tumor cells and the biological half-life of ^{131}I in the body. While the uptake of radioiodide into the thyroid gland is associated with organification and prolonged retention of iodide in this tissue, long-term radiation exposure of normal thyroid cells results in induced hypothyroidism [74].

Another critical issue following the administration of ^{131}I for extra-thyroidal cancer is the optimization of the appropriate dose to avoid delivering a higher dosage of the radioisotope to other tissues, particularly the thyroid gland [75]. In extra-thyroidal tumors, iodide is not efficiently incorporated into proteins, resulting in shorter iodide retention, unlike in the thyroid glands. The longer retention time of radioiodine in tumor cells increases the duration of radiation exposure within the cell. The retention time of radioiodide in serum is almost three times longer in human extrathyroidal tumors than in rodents, which resulted in a higher radiation dose of ^{131}I in humans with NIS -expressing tumors [76, 77]. However, it may be possible to enhance the biological effect of ^{131}I by inhibiting the repair of DNA double-strand breaks (DSBs), which are considered the most lethal form of DNA damage [78]. This could potentially address some of the limitations of ^{131}I therapy in the treatment of NIS-transduced extra-thyroidal cancer. Moreover, in exogenously NIS-transduced tumor tissue after thyroid sequestration, radioiodide absorption in thyroid tissue may be reduced, which in turn leads to a high therapeutic effect of radioiodide in the target tumor cell.

Although no evidence has yet been provided for the common use of external iodide to suppress NIS function in the normal thyroid, pretreatment supplementation KI appears to be a more pragmatic solution for blocking iodide uptake in the thyroid gland for NIS-mediated ^{131}I therapy in extra-thyroidal cancer [13].

Another problem with the empirical activity strategy is the fact that the influence of radioiodine function does not depend directly on the absorbed dose, but depends on various factors such as the homogeneity of radioiodine uptake by the cells, the iodine deficiency of the body before treatment and the TSH level, the excretion rate of radioiodine, and finally the biology of the tumor.

According to the preclinical studies mentioned in this review, the inherent ability of viral vectors to insert their genetic material into host cells has led them to receive special attention, as have adenoviral vectors for NIS-mediated ^{131}I therapy. However, cancer gene therapy with non-replicating adenoviral vectors, based on initial clinical trials, has its limitations. These include high potency immunogenicity, deprivation of non-transduced tumor cells from the therapeutic effects of the vectors, and high incidence of leukemia due to uncontrolled insertion of DNA into the host genome [29].

The use of HSP70B-NIS-MSCs has worked well in most animal studies, including Mariella Tutter's group. However, in some animal studies, the effect was lower due to the less homogeneous response of tumors to hyperthermia. Although this problem is less addressed in clinical studies, as hybrid magnetic resonance therapy with high-intensity focused ultrasound is now used for hyperthermia therapy of tumors. In addition to effective radioiodine therapy through NIS transgenes in non-viral delivery methods such as genetically modified MSCs in the treatment of breast cancer or extracellular vesicles in preclinical hepatocellular carcinoma [13], MSCs have also been shown to trigger or amplify tumors, as demonstrated by a number of studies with ovarian [79], melanoma [80], breast [81], and other tumor cells. In this regard, engineering and administration of immune cells could be an alternative to reduce unwanted side effects of MSCs.

Conclusion

The application of NIS-mediated radionuclide therapy is a rapidly developing field that has shown promising results in extra-thyroidal tissues. Currently, a variety of systemic NIS transfer methods are being investigated in preclinical studies, including viral vectors, engineered MSCs, and polyplex-mediated NIS. NIS as a theranostic gene facilitates spatial and temporal noninvasive imaging, dose optimization, and interpretation following therapeutic radionuclide application. Even though iodide accumulation and retention are constant arguments against effective NIS gene delivery, studies have shown that this level is sufficient to elicit significant antitumor responses. The levels of exogenous expression of NIS by different platforms in the quiescent and/or hypoxic tumor microenvironment is another aspect that needs to be thoroughly investigated in preclinical experiments. Meanwhile, non-invasive imaging techniques such as PET and SPECT have provided a high-resolution and highly sensitive tool to optimize therapeutic regimens.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval Not applicable.

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