Journal of Endocrinology and Thyroid Research
ISSN: 2573-2188

Juniper Publishers
key to the Researchers

Mini Review
Volume 7 Issue 3 - July 2023
DOI: 10.19080/JETR.2023.07.555712

J Endocrinol Thyroid Res

Lessons Learned from the Thyroid: Use of Nis for Non-Thyroideal Pathologies

Ana Redrado Osta[1]#, Belén Azanza-Hernández[2]# and Pilar Martin Duque[1,2,3]

[1]*Instituto de Investigación Sanitaria (IIS) de Aragón, Avenida San Juan Bosco, Zaragoza, Spain*

[2]*Surgery and Chemical and Environmental Engineering departments; University of Zaragoza, Spain*

[3]*Networking Research Center in Biomaterials, Bioengineering and Nanomedicine (CIBER-BBN), Instituto de Salud Carlos III, Spain*

Submission: June 20, 2023; **Published:** July 19, 2023

#Both authors have contributed equally

***Corresponding author:** Pilar Martin Duque, Department of Surgery, University of Zaragoza, Spain. Email: mariadelpilar.martin@unizar.es

Abstract

Over the years, sodium iodine symporter. (NIS) has been studied and exploited for thyroid cancer (and other thyroidal pathologies) diagnosis and treatment. Thanks to the cDNA cloning of the NIS gene and the many advances in gene transfer strategies, NIS has become a powerful tool to monitor and treat numerous non-thyroidal cancer types.

Keywords: NIS; iodide isotopes; imaging; radiotherapy; gene transfer; oncolytic virus; radio virotherapy; nanoparticles

Abbreviations: NIS: sodium iodide symporter; DTC: Differentiated thyroid cancer; PET: positron emission tomography; SPECT: single-photon emission computed tomography; RAI: Radioactive Iodine Therapy; CRAds: conditionally replicating adenoviruses; MV: measles virus

NIS In Physiological Conditions and Its Role on Differentiated Thyroid Cancer Treatment

Nowadays, the sodium iodide symporter (NIS) is known to be key in the mechanism of iodide for the thyroid hormones synthesis process. NIS is a transmembrane protein expressed on the basolateral surface of thyroid follicular cells and is responsible for the active transport of iodine thanks to the sodium transport following the concentration gradient [1]. There have been many crucial advances to establish the current clinical scenario regarding thyroid pathologies. In 1940, ^{131}I was administered for the first time as a hyperthyroidism treatment and in 1946 it was employed to treat thyroid cancer [2]. Moreover, over the years, NIS transporter has gained importance as a valuable imaging tool [3]. The choice of *imaging modality* employed in thyroid cancer varies upon the expression of sodium iodide symporter (NIS) in tumor cells and the availability of specific radioisotopes. Consequently, the selection varies depending on the specific radioisotope utilized. In DTC (Differentiated thyroid cancer), non-invasive single-photon emission computed tomography (SPECT) imaging technique can be utilized to detect photon-emitting radionuclides, including $^{123/125/131}$I and ^{99m}TcO4, which are transported intracellularly by NIS for medical diagnostic purposes.^{123}I exhibits suitability as a radioisotope for SPECT imaging, like ^{99m}TcO4. Nevertheless, ^{99m}TcO4 possesses a short half-life, yet it is not abundantly available. Within the context of SPECT imaging, the utilization of a radioisotope with a short half-life is advantageous. The sodium/iodide symporter (NIS), it exhibits the capability to transport radioisotopes for medical-clinical purposes, such as ^{124}I and [^{18}F]-tetrafluoroborate (^{18}F-BF4-).

But besides their radiotherapeutic effect it was demonstrated that these radioisotopes can be effectively detected utilizing the highly sensitive non-invasive imaging technique known as positron emission tomography (PET). The utilization of ^{124}I for PET imaging entails enhanced sensitivity in comparison to single-photon emission computed tomography (SPECT). However, it is worth noting that ^{124}I emits both positrons and gamma radiation, thereby potentially compromising the quality of the acquired images. Consequently, significant attention has been devoted to the radioisotope ^{18}F-BF4 as it stands out as the most promising candidate for imaging purposes. Its substantial positron emission capacity coupled with its low energy characteristics allows for the acquisition of high-quality three-dimensional PET images [4].

NIS is also involved in the success of *RAI therapy* (Radioactive Iodine Therapy). ^{131}I emits both beta particles and photons with higher energy levels compared to the radioisotopes, thereby resulting in inferior image quality when contrasted with other radioisotopes but a great effect as radiotherapy against the tumours.

In relation to ^{131}I, it harnesses high-energy nuclear electron emissions that possess the capacity to effectively eliminate target cells. Nevertheless, this radiation exerts detrimental effects on DNA integrity, impacting not only the intended target cells but also the surrounding cellular milieu, culminating in the formation of DNA cross-links, breaks, and base lesions [5].

The introduction of NIS as a diagnostic treatment and/or monitoring tool in thyroid pathologies has entailed a magnificent advance in clinical practice. The idea of making use of this approach in non-thyroidal tissues offers the opportunity of applying all the expertise acquired over the years to numerous pathologies [6]. Considerable efforts were dedicated to the study and validation of different strategies to transfer functional NIS to other tissues. Herein, we provide a summary of some.

NIS In Viral Vectors. Viruses as Gene Transfer Agents for Non-Thyroidal Tumours

The use of viruses as viral vectors represents a highly promising strategy for antitumor therapy, transferred the desired therapeutic gene. A novel approach involves the targeted transfer of the NIS gene to non-thyroidal tumours, enabling the utilization of both NIS-guided imaging techniques and the therapeutic application of radioisotopes. On the one hand, in many cases, replication-defective vectors were used. For those cases, even though they are unable to induce cell lysis, they allow for the insertion of therapeutic genes into the cellular genome. On the other hand, oncolytic viruses are highly promising as they possess distinct characteristics that enables the implementation of radio virotherapy, besides to the cell death induced by the viral replication [7].

One of the most widely studied oncolytic viruses for NIS gene transfer therapy strategies is *measles virus (MV)*. An attenuated MV vaccine strain has been proven to have an extraordinary safety profile. Tumour selectivity of this virus is achieved through the CD46 specific binding to tumour cells [8]. The utilization of MV-NIS as a reporter/therapy strategy has been successfully validated across several types of cancers. In a multiple myeloma xenograft mouse model, Russell's team showed tumoral regression upon a single i.v. injection of MV-NIS when ^{131}I was administered [9]. Moreover, prostate cancer xenografts derived from the LNCaP cell line were shown to be destroyed when MV-NIS was locally or systemically administered, and the therapeutic effect could also be enhanced with ^{131}I administration [10]. Finally, for pancreatic cancer, the capacity of single-photon emission computed tomography/computed tomography (SPECT/CT) to determine the distribution pattern within the tumour and monitor the infection of oncolytic MV-NIS viruses [11].

MV is not the sole virus employed for NIS gene transfer, other oncolytic viruses have been explored with a similar approach. *Vaccinia virus* in combination with NIS (VV-NIS) and iodide administration has been shown to be effective in different cancer models such as in endometrial cancer [12] or gastric cancer [13]. Moreover, VV-NIS could be used as an imaging tool to detect remaining cancer cells in the margins of resected breast cancer tumours in murine models [14]. Other two oncolytic viruses which have been employed are *poxvirus and vesicular stomatitis virus*; those approaches have demonstrated to have positive effects in an HCT116 colon cancer xenograft mouse model [15] and in hematological malignancies as in immunocompetent mice with syngeneic 5TGM1 myeloma tumours [16], respectively. Noteworthy are the viruses based on conditionally replicating *adenoviruses* (CRAds). NIS has been widely used for NIS transfer on CRAds for imaging and therapy. Vassaux's group described several viruses [17, 18] under several promoters driving the viral replication on different populations and type of tumors. NIS-Ads were also used to track stem cells on their migration to the tumors [19] with promising results.

Nanoparticles and NIS in Therapy

The relationship between the sodium/iodide symporter (NIS) and nanoparticles is based on their potential applications for medicine and imaging. Consequently, researchers have investigated the utilization of the NIS transporter in conjunction with nanoparticles to facilitate targeted drug delivery [20]. This approach involves attaching nanoparticles to specific ligands capable of binding to the NIS transporter, enabling the direct administration of radioisotopes to cells expressing this transporter [21]. Urnauer's team [22] conducted in vitro and in vivo studies to assess the capability of the B6 ligand in NIS gene delivery. In conjunction with LPEI-PEG/NIS *polyplexes* (specifically LPEI-PEG-B6/NIS), they successfully demonstrated enhanced iodide uptake in the tumor and significant accumulation of radioiodine in tissues expressing NIS physiologically, thereby confirming its high tumor specificity and ligand-dependent uptake. The study conducted by Le Goas and colleagues aimed to evaluate the capacity to radiosensitizer neoplasms using nano therapy in combination with standard systemic radioiodine therapy [23]. For this purpose, gold nanoparticles (AuNPs) were chosen and administered in conjunction with standard systemic radioiodine therapy, with a perspective towards clinical translation. *Gold nanoparticles* (AuNPs) were selected to enhance the lethal efficacy of iodine-^{131} in two types of tumor cells genetically modified to express NIS [24]. In the case of colorectal cancer cells (DHD-NIS), the analyses indicated a higher concentration of gold compared to the B16-NIS melanoma cells, significantly decreasing the 50% lethal dose in DHD-NIS cells. Furthermore, the enrichment of tumors with PMAA-AuNPs prior to ^{131}I therapy led to a more effective inhibition

How to cite this article: Ana Redrado O, Belén Azanza-H, Pilar Martin D. Lessons Learned from the Thyroid: Use of Nis for Non-Thyroideal Pathologies. J Endocrinol Thyroid Res. 2022; 7(3): 555712. DOI: 10.19080/JETR.2023.07.555712

of tumor growth [25], creating new perspectives for the use of metallic nanoparticles in molecular radiation therapy, not only in ^{131}I-based treatment but also in other radiotherapeutic therapies. Finally, the use of *dendrimers* bound to a DNA plasmid carrying NIS showed promising results both for diagnostic and therapy [26].

The fusion of the NIS transporter with nanoparticles offers numerous advantages, including targeted drug delivery, enhanced therapeutic effectiveness, diminished systemic side effects, and the ability to non-invasively image specific tissues. However, it is important to note that this field is still evolving, with ongoing research shaping the application of the NIS transporter and nanoparticles in medicine and imaging. Consequently, the specific details and advancements in this area may vary as new studies and discoveries emerge.

Final Remarks

The examination of the NIS transporter in conjunction with viral and non-viral vectors for cancer therapy and diagnostic in unrelated non-thyroid pathologies represents a relatively underexplored area of research harboring significant prospect. The application of these vectors and their subsequent implementation of radiotherapy signifies a remarkable advancement for the treatment of diverse pathologies, marking a pivotal milestone in cancer research.

Acknowledgment

P.M-D´s lab is funded by Instituto de Salud Carlos III (ISCIII) (PI19/01007 and DTS21/00130) and AECC and ASPANOA. We also thank CIBER-BBN, an initiative funded by the VI National R&D&i Plan 2008–2011 financed by the Instituto de Salud Carlos III (ISCIII) with the assistance of the European Regional Development Fund. A. R-O is funded by the Aragon Government Ph.D. Grant and cofounded by Aragon/FEDER 2014–2020 “Building Europe from Aragon” and B. A-H by INVESTIGO program.

References

1. Paroder Belenitsky M, Maestas MJ, Dohán O, Nicola JP, Reyna Neyra A, et al. (2011) Mechanism of anion selectivity and stoichiometry of the Na+/I- symporter (NIS). Proceedings of the National Academy of Sciences of the United States of America 108(44): 17933-17938.
2. Hertz S, Roberts A, Means JH, Evans RD (1940) Radioactive iodine as an indicator in thyroid physiology. J Pharmacol Exp Ther 128: 565-576.
3. Seidlin SM, Marinelli LD, Oshry E (1946) Radioactive iodine therapy: effect on functioning metastases of adenocarcinoma of the thyroid. JAMA 132: 838-847.
4. Miller A, Russell SJ (2016) The use of the NIS reporter gene for optimizing oncolytic virotherapy. Expert Opin Biol Ther 16: 15-32.
5. Portulano C, Paroder-Belenitsky M, Carrasco N (2014) The Na+/I-symporter (NIS): mechanism and medical impact. Endocrine reviews 35(1): 106-149.
6. Baril P, Martin Duque P, Vassaux G (2010) Visualization of gene expression in the live subject using the Na/I symporter as a reporter gene: applications in biotherapy. Br J Pharmacol 159(4): 761-771.
7. Penheiter AR, Wegman TR, Classic KL, Dingli D, Bender CE, et al. (2010) Sodium iodide symporter (NIS)-mediated radio virotherapy for pancreatic cancer. American journal of roentgenology 195(2): 341-349.
8. Msaouel P, Opyrchal M, Dispenzieri A, Peng KW, Federspiel MJ, et al. (2018) Clinical Trials with Oncolytic Measles Virus: Current Status and Future Prospects. Current cancer drug targets 18(2): 177-187.
9. Dingli D, Peng KW, Harvey ME, Greipp PR, O'Connor MK, et al (2004) Image-guided radio virotherapy for multiple myeloma using a recombinant measles virus expressing the thyroidal sodium iodide symporter. Blood 103(5): 1641-1646.
10. Msaouel P, Iankov ID, Allen C, Aderca I, Federspiel MJ, et al. (2019) Noninvasive imaging and radio virotherapy of prostate cancer using an oncolytic measles virus expressing the sodium iodide symporter. Mol Ther 17: 2041-2048.
11. Penheiter AR, Wegman TR, Classic KL, Dingli D, Bender CE, et al. (2010) Sodium iodide symporter (NIS)-mediated radio virotherapy for pancreatic cancer. AJR American journal of roentgenology 195(2): 341-349.
12. Liu YP, Wang J, Avanzato VA, Bakkum Gamez JN, Russell SJ, et al. (2014) Oncolytic vaccinia virotherapy for endometrial cancer. Gynecologic oncology 132(3): 722-729.
13. Jun KH, Gholami S, Song TJ, Au J, Haddad D, et al. (2014) A novel oncolytic viral therapy and imaging technique for gastric cancer using a genetically engineered vaccinia virus carrying the human sodium iodide symporter. Journal of experimental & clinical cancer research: CR 33(1): 2.
14. Gholami S, Chen CH, Belin LJ, Lou E, Fujisawa S, et al. (2013) Vaccinia virus GLV-1h153 is a novel agent for detection and effective local control of positive surgical margins for breast cancer. Breast cancer research: BCR 15(2).
15. Warner SG, Kim SI, Chaurasiya S, O'Leary MP, Lu J, et al. (2019) A Novel Chimeric Poxvirus Encoding hNIS Is Tumor-Tropic, Imageable, and Synergistic with Radioiodine to Sustain Colon Cancer Regression. Molecular therapy oncolytics 13: 82-92.
16. Goel A, Carlson SK, Classic KL, Greiner S, Naik S, et al. (2007) Radio iodide imaging and radio virotherapy of multiple myeloma using VSV(Delta51)-NIS, an attenuated vesicular stomatitis virus encoding the sodium iodide symporter gene. Blood 110(7): 2342-2350.
17. Riesco-Eizaguirre G, De la Vieja A, Rodríguez I, Miranda S, Martín Duque P, et al. (2011) Telomerase-driven expression of the sodium iodide symporter (NIS) for in vivo radio iodide treatment of cancer: a new broad-spectrum NIS-mediated antitumor approach. J Clin Endocrinol Metab 96(9): 1435-1443.
18. Merron A, Baril P, Martin Duque P, de la Vieja A, Tran L, et al. (2010) Assessment of the Na/I symporter as a reporter gene to visualize oncolytic adenovirus propagation in peritoneal tumours. Eur J Nucl Med Mol Imaging. 37(7): 1377-1385.
19. Belmar-López C, Vassaux G, Medel-Martinez A, Burnet J, Quintanilla M, et al. (2022) Mesenchymal Stem Cells Delivery in Individuals with Different Pathologies: Multimodal Tracking, Safety and Future Applications. Int J Mol Sci 23(3):1682.
20. Briolay T, Petithomme T, Fouet M, Nguyen Pham N (2021) Delivery of cancer therapies by synthetic and bio-inspired nano vectors. Molecular cancer 20: 1-24.
21. Hua S, de Matos MBC, Metselaar JM, Storm G (2018) Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization. Front Pharmacol 9:790.

How to cite this article: Ana Redrado O, Belén Azanza-H, Pilar Martin D. Lessons Learned from the Thyroid: Use of Nis for Non-Thyroideal Pathologies. J Endocrinol Thyroid Res. 2022; 7(3): 555712. DOI: 10.19080/JETR.2023.07.555712

22. Urnauer S, Klutz K, Grünwald GK, Morys S, Schwenk N, et al. (2017) Systemic tumor-targeted sodium iodide symporter (NIS) gene therapy of hepatocellular carcinoma mediated by B6 peptide polyplexes. The journal of gene medicine 19(5): 2957.

23. Le Goas M, Paquet M, Paquirissamy A, Guglielmi J, Compin C et al. (2019) Improving 131I radioiodine therapy by hybrid polymer-grafted gold nanoparticles. International Journal of Nanomedicine 7933-7946.

24. Rosa S, Connolly C, Schettino G, Butterworth KT, Prise KM (2017) Biological mechanisms of gold nanoparticle radio sensitization. Cancer Nanotechnol 8(1):2.28217176

25. Zhang L, Chen H, Wang L (2010) Delivery of therapeutic radioisotopes using nanoparticle platforms: potential benefit in systemic radiation therapy. Nanotechnol Sci 3: 159–170.24198480

26. Chisholm EJ, Vassaux G, Martin Duque P, Chevre R, Lambert O, et al. (2009) Cancer-specific transgene expression mediated by systemic injection of nanoparticles. Cancer Res 69(6): 2655-2662.

DOI: 10.19080/JETR.2023.07.555712

How to cite this article: Ana Redrado O, Belén Azanza-H, Pilar Martin D. Lessons Learned from the Thyroid: Use of Nis for Non-Thyroideal Pathologies. J Endocrinol Thyroid Res. 2022; 7(3): 555712. DOI: 10.19080/JETR.2023.07.555712