Sodium Iodide Symporter (NIS) in the Management of Patients with Thyroid Carcinoma

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Abstract

Although radioiodine has been applied in thyroid diseases including carcinoma for over 70 years, it was only in 1996 that the basic molecular mechanism of iodine uptake was identified. Iodide is actively transported into the thyroid via a membrane glycoprotein known as sodium iodide symporter (NIS). NIS mediates radioiodine uptake into thyroid normal and cancer cells. The knowledge on NIS expression has provided scientific background to the empirical management of thyroid carcinoma. Based on recent studies of the NIS gene, this paper provides current clinical applications and future studies.

Keywords Sodium iodide symporter · NIS · Thyroid cancer · Gene therapy · Theranostics

Clinical Application

Differentiated thyroid cancer (DTC) is one of the most common cancers especially in Korea and Japan [1]. The 10-year survival rate for DTC ranges from 80 to 95% [2]. However, 5 to 20% of DTC patients have metastases usually to the lung and the bone which decreases the 10-year survival rate by 50% [3]. Our group found that NIS expression was positively related to the radioiodine treatment result in these patients. Analysis and enhancement of NIS expression can provide more proper and precise management of thyroid cancer. We suggested that immunohistochemical analysis of NIS protein in tumor tissues should be essential in determining radioiodine treatment in case of recurrence or metastases [4].

We found that the expressions of NIS and glucose transporter-1 genes were inversely related in papillary thyroid cancer tissues [5]. NIS gene expression was higher in relatively well-differentiated thyroid cancer than the expression in less differentiated thyroid cancer which induced high sensitivity of radioiodine scan and low sensitivity of FDG PET in detection of metastases. This was the opposite in the case of less differentiated thyroid cancer [6]. These results provide a

proper strategy for radioiodine therapy and non-radioiodine therapies including resection, drug, and radiotherapy.

Measurement of NIS expression can be applied to find redifferentiation agents in less differentiated thyroid cancer. Until now, radioiodine therapy combined with retinoic acid has been implemented for redifferentiation and restoration of NIS expression [7]. Further agents and tyrosine kinase inhibitors have been investigated and agents stimulating translocation of NIS protein to the cell membrane are being developed.

Recently, we found that the expression of NIS was different not only between metastatic and primary cancer cells but also between metastatic sites [8]. So et al. reported that NIS expression level in more than half of the metastatic sites did not match to their primary tumors. In addition, NIS expression levels within recurrent lymph nodes did not match one another in the same patient [8]. While the prognosis of thyroid cancer is very excellent, the cause of death lies in local problems including malignant pleural effusion and aspiration pneumonia following swallowing difficulty. Thus, proper management of individual tumor sites should be important. This suggests a need for lesionalized therapy to thyroid cancer beyond the current empirical and personalized therapy in cancer management. In vitro molecular diagnostics cannot be a diagnostic method of choice because multiple and repeated tissue biopsies are not suitable. As a result, molecular imaging is crucial in identifying heterogeneous expression of NIS in primary and metastatic tumor sites because it is noninvasive and repetitive. Recent technological advance in imaging instruments like PET/CT and SPECT/CT makes this lesionalized therapy possible to provide exact localization of pathologic sites [9, 10].

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Radioiodine Gene Therapy

Gene therapy inserts a gene into patient's cells to replace, inactivate, or knock out a preexisting mutated gene. Although gene therapy carries a lot of potential, unexpected human deaths from early clinical trials have halted the gene therapy study until now [11]. Alternative methods for gene transfer such as non-viral vector transfection are constantly being proposed and investigated showing high possibility.

One of the applied modified gene therapies involves radionuclide gene therapy which combines gene therapy along with radioiodine therapy. Transfection of the NIS gene can induce expression of NIS in cell membrane, resulting in the accumulation of I-131. Several experiments have reported successful results, but no clinical trials have been conducted up to this date. To enhance therapeutic effect, we added p53, thyroid peroxidase (TPO), or transcriptional factors directly into thyroid carcinoma cells. Results have shown the potential of NIS-mediated radionuclide therapy for both thyroid and non-thyroid cancers [12].

Furthermore, our group developed a highly efficient human NIS gene (opt-hNIS) by implementing a method known as codon optimization. We altered gene sequences to contain the highest frequency of codons for tRNAs in the host organism to maximize the amount of protein synthesis. The efficacy of opt-hNIS was tested by using mouse xenograft models with cancer cells expressing human NIS (hNIS) or opt-hNIS. As a result, opt-hNIS showed high NIS expression by two or three times that of the normal hNIS, suggesting an improved therapeutic effect of opt-hNIS [13].

Conclusion/Suggestion

Research results on NIS have been successful in providing scientific background to the current empirical knowledge of the thyroid cancer management. Combined molecular imaging methods provide the presence of metastasis or recurrence as well as other valuable information about treatment modality and prognosis of certain treatment. More precise and proper treatment of thyroid cancer has been made possible through enhancing NIS expression in clinical applications. Radioiodine scan and therapy targeting NIS were the first clinical applications of theranostics. By expanding the application of NIS in future clinical studies, we can enhance the accuracy and efficacy of thyroid cancer management. Establishing intimate and dedicated cooperation between scientists and clinicians can solve clinical problems in the management of thyroid cancer.

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Compliance with Ethical Standards

Conflict of Interest June-Key Chung, Hyun Woo Kim, Haewon Youn, and Gi Jeong Cheon declare no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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