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Evaluating the Natrium Iodide Symporter Expressions in Thyroid Tumors

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Abstract

BACKGROUND: Decreased Natrium iodide symporter (NIS) expression levels or diminished NIS targeting thyroid cancer cells' plasma membrane leads to radioiodine-refractory disease.

AIM: The aim of this study was to analyze the NIS expression in thyroid tumors.

MATERIALS AND METHODS: The samples were thyroid tissues of patients who underwent surgery for a thyroid tumor. The tissues were processed for NIS protein expressions by immunohistochemistry (IHC) and Western blot (WB). Graves' disease samples were used as positive controls. The samples were incubated without the primary antibody, and they were used as negative controls for IHC examination. Na+/K+ ATPase was a plasma membrane protein marker in the WB procedure.

RESULTS: Twenty-nine samples were assessed for NIS protein. All of them showed the expression in the cytoplasm with intensity 1+ to 3+ with Allred score 3-8. Fourteen out of 29 cases (48.2%) showed NIS cytoplasm staining intensity ≥2+ consist of 10 papillary thyroid cancer (PTC), three follicular thyroid cancer, and one adenoma. Membrane staining was found in 2 samples of PTC (6.9%). Six samples (adenoma 1 sample, PTC 5 samples) showed NIS expression at membrane very weak (1+); they were considered as negative. NIS protein has several bands of ~ 80 kDa, ~ 62 kDa, and ~ 49 kDa.

CONCLUSION: NIS expression in thyroid cancer mostly expresses in the cytoplasm instead of the membrane. NIS will play a functional role in the membrane to bring iodine across the membrane against the concentration. It can be the main reason for the lack of response of radioiodine in some differentiated thyroid cancers.

Introduction

One of the most common endocrine neoplasms is thyroid cancer [1]. In most countries, thyroid cancer incidence rate has increased, and it does have a steady mortality rate [2], [3], [4], [5]. Thyroid cancer is the eleventh rank cause of deaths from cancer [6]. This cancer incidence is rapidly increasing in developed countries compared to developing countries in females and males [7]. The rising of advanced detection technologies and changing lifestyles in developed countries can be the reasons.

The follicular and parafollicular thyroid cells are two primary parenchymal cells of thyroid cancer origin. These can rise to be well-differentiated thyroid cancer (DTC) such as papillary and follicular types. Well-differentiated is the majority incidence of thyroid cancer, papillary (80%) and follicular (10%). Then, it is followed by poorly DTC, medullary (5-9%), and anaplastic (2%) [8]. DTC is associated with a good prognosis.

Radioiodine (^{131}I) has been used for adjuvant therapy to manage well-DTC for more than 60 years. Beta (β)-emitting of ^{131}I is used to destroy remaining thyroid cells post-thyroidectomy included metastases [9], [10], [11], [12], [13]. It is relatively un-expensive and widely available. It increases up to 80% of the 10-year survival rate and decreases the death number compared to patients who had not received ^{131}I (3%: 12%) [14], [15]. On the other hand, some thyroid cancers and metastases showed low uptake of ^{131}I compare to healthy thyroid tissues [16]. One-third of advanced DTC metastases show low avidity to iodine [8], [17], [18], [19]. Losing the ability to concentrate iodine can occur during the progression of the disease.

Iodine is transporting into follicular thyroid cells against the electrochemical gradient. In a normal condition, a gradient between a thyroid cell and an extracellular is 100:1 [20]. Natrium iodide symporter (NIS) is used for iodine to cross the cell membrane. It resides in the thyroid in the basolateral membrane of epithelial cells and transports two cations of sodium (Na+) and one anion of iodide (I-) into the cells. This process is facilitated by an enzyme Na+/K+ ATPase [21], [22], [23].

Decreased NIS expression levels or diminished NIS targeting to thyroid cancer cells' plasma membrane lead to radioiodine-refractory disease. The main reason for impaired of ^{131}I uptake is defective of NIS expression [15], [17], [23], [24]. This study aims to analyze the NIS expression in thyroid tumors.

Materials and Methods

The samples were thyroid tissues of patients who underwent surgery for thyroid diseases during June to September 2017. Twenty-nine samples were classified as thyroid diseases, according to the World Health Organization recommendation by pathologists using hematoxylin and eosin staining [25]. The tissues were processed at the Pathology Anatomy Department of Faculty of Medicine Universitas Andalas. If the samples were not possible to process quickly, they were stored at –4°C. NIS protein expressions were analyzed by immunohistochemistry (IHC) and Western blot (WB) studies. Ethical approval was obtained from the Ethics Committee of Medical Faculty of Universitas Andalas # 357/KEP/FK/2017.

IHC

Paraffin blocks cut into 4 mm slices and placed on microscope slides. These were then deparaffinized, rehydrated, and incubated with sodium iodide symporter antibody (FP5A, Thermo Scientific) at a 1:200 dilution for 60 min at room temperature. The slides were rinsed in phosphate-buffered saline and incubated in a Starr Trek Universal HRP Detection Kit for 15 min. Then, they were incubated using a diaminobenzidine detection kit. Graves' disease samples were used as positive controls. The samples were incubated without the primary antibody, and they were used as negative controls.

All slides were evaluated by light microscopy. The level of NIS expression was analyzed by three pathologists. Samples were examined in tumor areas. The membrane expression was scored using a scale of 0 to 3+ according to HER2/neu staining criteria. A score of 0 if no stain at the membrane, score 1+ if the membrane was staining more than 10% cell population. A score of 0 or 1 was considered negative. Score 2+, if moderate staining >10% cell population and 3+ strong circumferential stainings >10% cell population. Score 2 and 3 were considered a positive result [26]. Cytoplasmic staining refers to the Allred technique with criteria; 0 if no staining, 1+ weak staining at the majority of the field of view, 2+ moderate, and 3+ strong staining. Intensity value was reported as staining intensity majority in all fields of view. The proportion of positive cells is the percentage of all cell positive stain regardless of the level of intensity. It was reported in percentage. Allred score was summation between proportion and intensity with score 0–8 [27].

WB

Membrane protein was isolated from thyroid samples. The membrane protein (100 μg) was added to the sample buffer (NuPAGE LDS sample buffer ×4, NuPAGE reducing Agent ×10, deionized water, Thermo Scientific) and heated for 10 min at 70°C. The protein was separated by SDS/PAGE (NuPAGE MOPS SDS buffer kit, Thermo Scientific), then transferred to a PVDF membrane (iBlot2 transfer stacks, Thermo Scientific) for 1.5 h. The blot stained to check protein on the membrane (SeeBlue Plus2, Thermo Scientific). Then, a blocking buffer was added to the membrane for 30 min to block nonspecific binding. It followed by incubating the membrane in monoclonal antibody sodium iodide symporter (FP5A, Thermo Scientific) 1:1000 at 4°C overnight. After three piles of washing, the membrane was incubated with secondary antibody 1:200 (goat anti-mouse IgG (H+L), Peroxidase Conjugate, Thermo Scientific) for 2 h at room temperature. Next, the membrane was covered with Horseradish peroxidase (1-step ultra tetramethylbenzidine-blotting solution). PVDF membrane was stripped and re-probed with Na+/K+ ATPase alpha antibody (M7-PB-E9, Thermo Scientific) as plasma membrane protein markers.

Statistical analysis

Experiments were performed in duplicate. Data and results are presented as the means ± standard deviations (SD). Kruskal–Wallis test and Mann–Whitney were used for data analysis, and $p < 0.05$ was considered statistically significant.

Results

Twenty-nine samples were analyzed from patients who underwent thyroidectomy. Two males and 27 females, and the mean age were 50.5 ± 10.5 years old. Papillary thyroid cancer (PTC) was 18 samples (62.1%), FTC three samples (10.3%), adenomas seven samples (24.2%), and Cyst one sample (3.4%) shown in Table 1.

IHC staining in thyroid tissues

Twenty-nine samples were assessed for NIS protein. All of them showed the expression in the cytoplasm with intensity 1+ to 3+ with Allred score

Table 1: Patients characteristics of thyroid tissues samples

S. No	Age	Gender	Sample	Histopathology	ATP ~ 80 kDa	NIS ~ 80 kDa	Membrane staining	Intensity	Cytoplasm proportion	Allred score
1	45	M	1P	Adenoma	+	+	-	+	90	6
2	33	F	4P	Cyst	+	-	-	+	90	6
3	47	F	5P	PTC	+	+	-	+	80	6
4	35	M	6P	PTC	+	-	-	++	80	7
5	42	F	7P	PTC	+	62 kDA	-	++	80	7
6	52	F	8P	PTC	+	+	-	+	70	6
7	46	F	9P	Adenoma	+	-	-	+	80	6
8	36	F	10P	PTC	+	+	-	++	70	7
9	62	F	11P	PTC	+	-	-	++	70	7
10	36	F	12P	Adenoma	+	+	+	++	80	7
11	49	F	13P	Adenoma	+	49 kDa	-	+	50	5
12	58	F	14P	PTC	+	+	+	++	90	7
13	48	F	15P	FTC	+	+	-	++	60	6
14	52	F	16P	PTC	+	+	-	+	70	6
15	74	F	17P	PTC	+	49 kDa	-	+	30	4
16	75	F	18P	FTC	+	+	-	++	80	7
17	52	F	19P	PTC	+	+	-	+	30	4
18	57	F	20P	Adenoma	NA	NA	-	+	20	3
19	45	F	21P	PTC	+	62 kDa	++	+	60	5
20	55	F	22P	PTC	+	-	+	+	50	5
21	36	F	23P	PTC	+	+	+	++	50	6
22	54	F	25P	PTC	+	49 kDa	+	++	60	6
23	52	F	26P	Adenoma	NA	NA	-	+	30	4
24	47	F	27P	PTC	NA	NA	-	+++	50	7
25	64	F	28P	PTC	+	+	++	++	80	7
26	51	F	29P	PTC	+	+	-	+	60	5
27	63	F	30P	FTC	+	+	-	++	80	7
28	52	F	31P	PTC	+	-	+	+++	90	8
29	47	F	32P	Adenoma	+	-	-	+	80	6

PTC: Papillary thyroid cancer, FTC: Follicular thyroid cancer, NIS: Natrium iodide symporter.

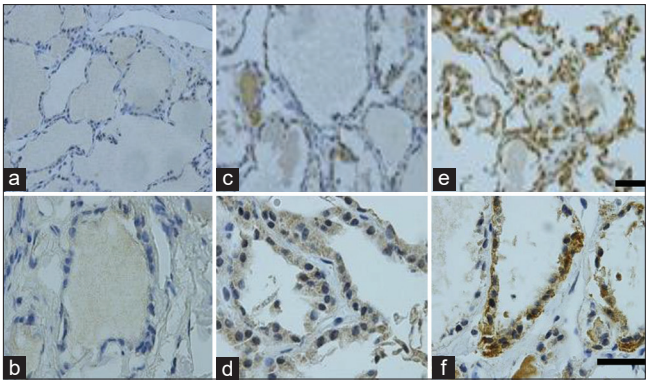

Figure 1: Cytoplasmic Natrium iodide symporter expression at follicle cell of adenoma goiter show a weak intensity (+) (a and b), moderate (++) (c and d), and strong (+++) (e and f). No staining at stromal and vascular. Most of the samples show NIS cytoplasmic intensity weak to a moderate level. Bar 100 µm

3–8. Fourteen out of 29 cases (48.2%) showed NIS cytoplasm staining intensity ≥2+, with Allred score 6-8 (mean 6.85±0.53), consist of ten PTC, three FTC and one adenoma (Table 1, and Figure 1a-f, 2a-f).

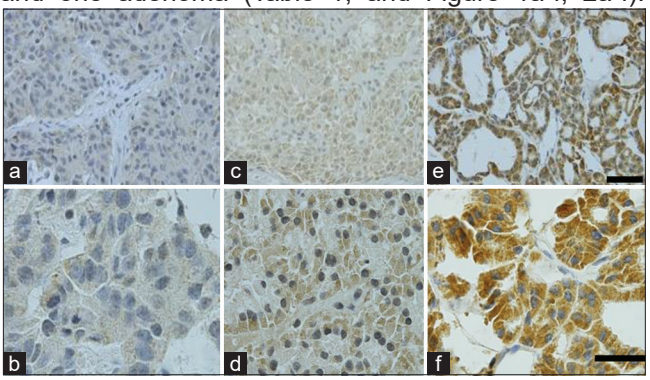

Figure 2: Cytoplasmic pattern of staining in thyroid cancer; weak (+) (a and b), moderate (++) (c and d), and strong (+++) (e and f). There is no staining at the stromal cell and vascular. The majority of samples demonstrate Natrium iodide symporter expression intensity weak to moderate. Bar 100 µm

Fifteen samples (51.7%) the cytoplasm staining 1+, with Allred score 3–6 (mean 5.13±0.99), consist of eight PTC, six adenomas, one cyst. The protein expression was not significantly different (p = 0.77) between intensity of staining and WB results (Figure 3). Membrane staining was found in two (6.9%) samples of PTC samples (Figure 4a-c). Six samples (adenoma one sample, PTC five samples) showed NIS expression at membrane very weak (1+); they were considered as negative.

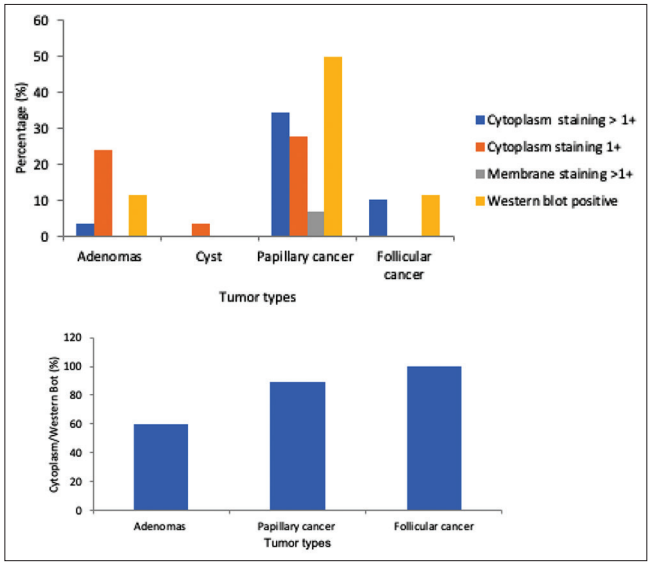

Figure 3: Natrium iodide symporter protein expressions based on thyroid disease types. The expression mostly in the cytoplasm in all types. Fourteen PTC samples expressed NIS in cytoplasm varying 1+ to 2+ with bands ~80, ~62, and ~49 kDa. Membrane positive staining is found in 6.9% samples of PTC, which correlated with molecule weight ~80 kDa. FTC samples expressed NIS protein in the cytoplasm with intensity >1+ have a band ~80 kDa (above). Protein expression was not significantly different between IHC and WB. Percentage of NIS protein expression in cytoplasm expression with WB results in adenomas, PTC, and FTC, 60%,89%, 100%, respectively (below)

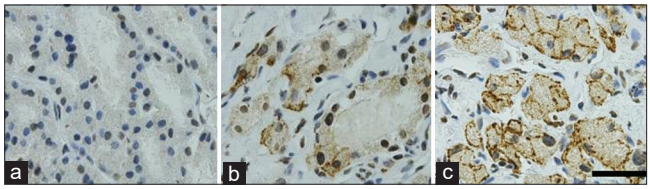

Figure 4: Pattern of the staining at the membrane. Negative Natrium iodide symporter expression (a), weak membrane expression and intensity (1+) (b), moderate staining (2+) (c). No stain at stromal cell and vascular. Bar 100 µm

WB analysis in thyroid tissues

NIS protein was analyzed in 26 of 29 thyroid samples because only the large tumor size could proceed with WB analysis. NIS protein is detected with molecule weight ~80, ~62, and ~49 kDa. The samples consist of 17 PTC, three FTC, five adenomas, and one thyroid cyst (Table 1). Nineteen samples expressed NIS protein, three adenoma samples, and 13 PTC three FTC samples. They migrated with a molecular weight of ~ 80 kDa in 14 samples and four samples with a molecular weight of ~ 62 kDa. Two samples expressed NIS protein at the membrane, migrate with a molecular weight of ~ 80 kDa and ~ 62 kDa (Figure 5). There was no significantly different the protein expression between WB and IHC results, with p = 0.25.

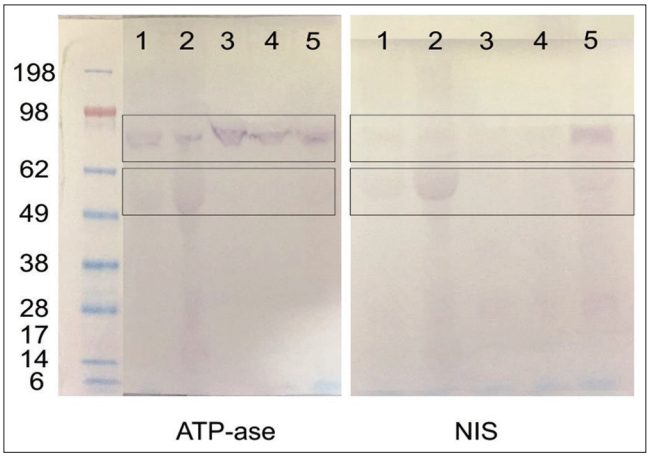

Figure 5: Natrium iodide symporter expression blotting result in thyroid tissues; the major band is detected with molecular weight ~80 kDa and several minor bands ~62, and ~49 kDa

Discussion

The classification samples were based on the histopathology examination. Seven of the samples were adenomas. All of them showed NIS protein expression in the cytoplasm in vary intensities (1+ to 3+). However, only one showed membrane expression 1+ with intensity in cytoplasm 2+, Allred scores 7, and the protein band ~80 kDa. The condition was also reported by other studies [28], [29], [30], [31]. The different staining intensity likely related to varying NIS protein expression in different thyroid sample types [31]. NIS protein is expressed in cytoplasm in all PTC and FTC, as shown in Table 1.

NIS protein major band with molecular weight ~80 kDa, and several minor bands with molecular weight approximately 62 kDa and 49 kDa. This report in line with other studies [28], [29], [30], [31], [32]. The minor bands can be a degradation fragment. However, further studies are needed to elaborate on this issue. NIS protein-membrane was expressed in 6.9% samples of PTC, one with a molecular weight of ~80 kDa and another ~62 kDa.

NIS expression levels are generally reduced in malignant thyroid tissue relative to normal tissue [16], [33]. It may result from multiple mechanisms elicited by several signaling pathways involved in thyroid tumorigenesis included genetic alternations [31], [34], [35]. Understanding the molecular background for thyroid cancer can lead to developing agents blocking the inappropriately activated pathway in cancer cells as a novel treatment strategy. Furthermore, NIS expression appears to be modulated by post-transcriptional events. A study reported that NIS is differentially expressed according to the tumor's genetic background [31]. However, the molecular mechanisms responsible for the downregulation of NIS in thyroid tumors remain poorly understood. On the other hand, NIS expression in the thyroid depends on inducing thyroid stimulation hormone (TSH), and low TSH levels affect ^{131}I uptake. It is known that TSH stimulates radioiodine uptake by DTC cells [16], [18]. It may be another factor that leads to reduced NIS expression and iodide-concentrating capacity in the thyroid cells.

^{131}I is generally effective for thyroid cancer. Two-thirds of thyroid cancer patients showed ^{131}I uptake, and one-third of thyroid cancer is reported low or negative uptake of ^{131}I, which has turned out to be ineffective [8]. Higher NIS expression is associated with higher uptake of ^{131}I by thyroid cell [18], [34]. Thyroid cells that do not respond to radioiodine can be lost NIS expression [15], [17], [23], [24]. The availability of specific polyclonal and monoclonal anti-hNIS antibodies has allowed the investigation of NIS protein expression levels in various thyroid tissues. Around 70–80% of thyroid cancers that express NIS are still well-differentiated regardless of their stage [30], [36], [37]. It seems that cell differentiation in thyroid cancer may associate with the NIS expression and radioiodine accumulation [35], [36]. Undifferentiated thyroid cancer cells unable to concentrate ^{131}I. It was assumed due to the absence of or low NIS expression [30], [38]. Impaired functional NIS can be the main reason for less response to a thyroid cancer cell to radioiodine. Some studies reported that NIS expresses mostly intracellular than at the plasma membrane [13], [18], [28], [29], [30], [31], [39].

A study reported that ^{131}I therapy's effectiveness does not solely depend on the amount of ^{131}I, in which transport is facilitated by NIS [39]. A^{131}I reduced breast

cancer cells (MCF7) proliferation in vitro, eventhough the cells did not express NIS protein [40], [41]. The condition can happen because the cell has its mechanism to the response of radiation [12], [13], [20], [42]. Another study reported that NIS expression might help characterize patients' risk with inadequate therapy response [31], [43]. Further research related to biological tumor behavior to radioiodine exposure included retrospective studies in large number series, is still needed.

Conclusion

NIS expression in thyroid cancer mostly expresses in the cytoplasm than the membrane. It can be one of the reasons for the ineffective radioiodine in some DTCs. To achieve an appropriate ^{131}I toxic effect without harming normal cells, translocation of NIS to the membrane may be one strategy that needs to consider tumor biology behavior. However, advanced studies of the NIS role in radioiodine transport are still needed.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors' Contributions

Aisyah Elliyanti: Performed the experiments, analyzed data, and drafted and edited this manuscript. Rony Rustam: Contributed in preparation methods and edit the manuscript. Tofrizal Tofrizal: Contributed analyzed data and writing the manuscript. Yenita Yenita: Analyzed data and edit the manuscript. Yayi D. Billianti Susanto: Analyzed data and edit the manuscript.

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