Sodium Iodide Symporter (NIS) Expression in Cytologically Indeterminate and Malignant Thyroid Nodules

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INTRODUCTION

- Well differentiated thyroid cancers vary significantly in their ability to concentrate radioiodine and, consequently, be accurately imaged and effectively treated with ^{131}iodine.
- The sodium iodide symporter (NIS) is a transmembrane glycoprotein (codified by the *SLC5A5* gene) expressed predominantly in the basolateral plasma membrane of thyroid follicular cells.
- NIS mediates the active transport of iodine from the bloodstream into thyroid follicular cells, playing an essential role in the treatment and monitoring of differentiated thyroid carcinomas when radioiodine therapy is indicated.
- The objective of this study was to evaluate the preoperative mRNA expression of NIS in FNA samples of cytologically indeterminate (Cyto I – Bethesda (B) III or IV) and suspicious for malignancy or malignant thyroid (B V and VI) nodules sent for molecular testing and associate its expression with genomic alterations.

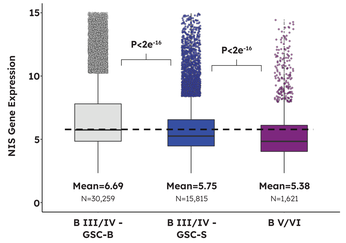
METHODS

- NIS mRNA expression was analyzed in 47,695 thyroid nodules sent for Afirma Genomic Sequencing Classifier (GSC) molecular testing.
- Differential NIS expression was explored across Afirma benign (GSC-B) and suspicious (GSC-S) categories, Bethesda cytology categories (B III-VI), and relative to various molecular alterations identified by the Afirma GSC and Xpression Atlas.

RESULTS

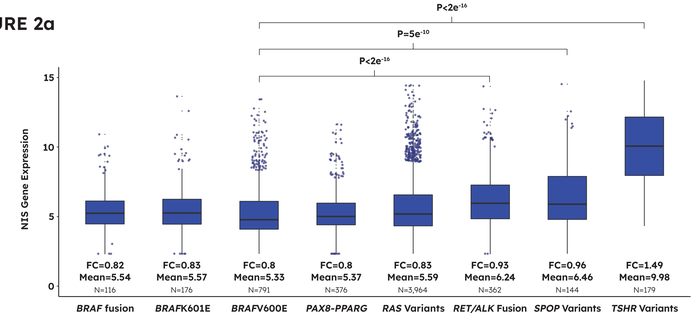
- Relative to B III/IV - GSC-B nodules, B III/IV - GSC-S and B V/VI nodules had lower NIS expression with a mean fold reduction (FC) 0.86 and 0.80 respectively ($p < 0.01$ for both) (Figure 1).
- Among B III/IV - GSC-S nodules (Figure 2a) and B V/VI nodules (Figure 2b), NIS expression was different based upon the presence of certain molecular alterations detected by Afirma XA. NIS expression was lowest in nodules with *BRAF*V600E variant expression and highest in nodules with *TSHR* variant expression.
- Nodules with a high Hürthle cell index (a component of the Afirma GSC core ensemble classifier) and high-risk molecular features of Hürthle cell carcinoma had lower NIS expression (Figures 3a and 3b).

FIGURE 1



Mean expression of the NIS gene was lower in B III/IV - GSC-S (suspicious) and B V/VI nodules as compared to B III/IV - GSC-B (benign). NIS expression was also lower in B V/VI as compared to B III/IV - GSC-S. (Wilcoxon rank-sum p-value < 0.001 for all.) Relative to GSC-B, GSC-S and Bethesda V/VI had a fold change (FC) 0.86 and 0.8, respectively.

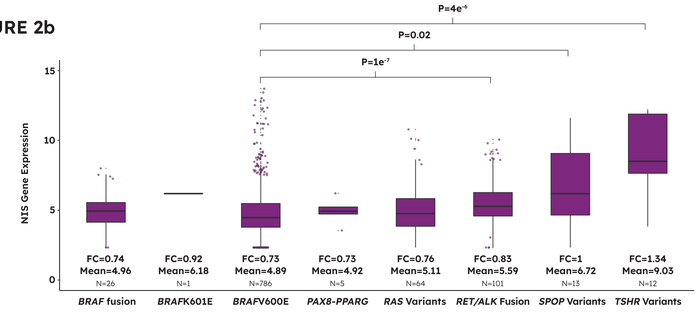
FIGURE 2a



Within GSC-S group, NIS was lowest in samples with *BRAF*V600E and highest in samples with Thyroid Stimulating Hormone Receptor (*TSHR*). Compared to GSC-B samples, nodules with *BRAF*V600E or *RAS* variants had lower expression (FC:0.80 and 0.84 respectively, $p<2e^{-16}$ for both), samples with *TSHR* variants had higher expression (FC:1.49, $p<2e^{-16}$), and *SPOP* variants and *RET/ALK* fusion were not different (FC:0.96 and 0.93 respectively).

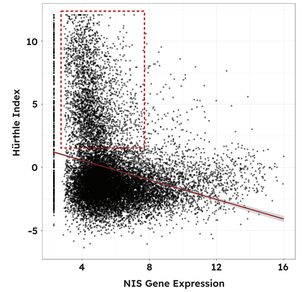
When evaluating NIS expression with relation to *BRAF*V600 in the GSC-S group, NIS expression was highest in samples with Thyroid Stimulating Hormone Receptor (*TSHR*) (FC:1.87 relative to *BRAF*V600E samples, $p<2e^{-16}$) variants, *SPOP* (FC:1.2, $p=5e^{-10}$), and *RET/ALK* fusion (FC:1.17, $p<2e^{-16}$). (Data not shown on graph.)

FIGURE 2b



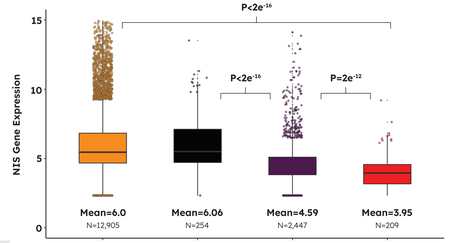
Within Bethesda V/VI nodules, NIS was lowest in samples with *BRAF*V600E and highest in samples with Thyroid Stimulating Hormone Receptor (*TSHR*). Relative to GSC-B samples, Bethesda V/VI nodules harboring *BRAF*V600E had lower NIS expression (FC:0.73, $p<2e^{-16}$), whereas samples with *TSHR* variants had higher expression (FC:1.34, p=0.003) and *SPOP* samples had no difference (FC:1, p=0.9).

FIGURE 3a



In BIII/IV GSC-S nodules, there is an inverse correlation between the Afirma Hürthle cell index and NIS expression across all tested nodules. Note that the red rectangle highlights that almost all samples with a Hürthle high index score have low NIS mRNA expression.

FIGURE 3b



Hürthle Index	LOW	HIGH	HIGH	HIGH
Neoplasm Index		LOW	HIGH	HIGH
LOH			LOW	HIGH

BIII/IV GSC-S samples with high Hürthle index, high neoplasm index, and high loss of heterozygosity (LOH) are more likely to be Hürthle cell carcinoma and these samples have the lowest NIS expression.

CONCLUSION

- NIS expression in indeterminate and malignant thyroid nodules varies across Bethesda cytology groups, Afirma GSC classification, and certain molecular alterations.
- NIS expression is necessary and may not be sufficient for thyroid tumor response to radioiodine.[1]
- To address the clinically relevant predictive significance of NIS mRNA expression levels in preoperative biopsy specimens, future studies should evaluate tumor iodine avidity and the response to radioiodine therapy.

REFERENCE

1. Tavares et al. *Endocr Connect.* 2018 Jan;7(1):78-90. PMID 29298843.