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Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR) Expression in Preoperative Thyroid Tumor Samples

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Potential conflict of interest may exist. Refer to the meeting app.

INTRODUCTION

- Thyroid cancer will account for ~2% of all new carcinoma diagnoses in the US in 2025.[3]
- Approximately 40,000 new cases of thyroid cancer are diagnosed in the US each year, and ~3000 of these patients die each year.
- An estimated 5-10% of patients have advanced thyroid cancer that is unresponsive to surgical and radioiodine therapy.[1]
- Retinoids influence cell growth and differentiation through retinoid receptors, retinoic acid (RAR) and retinoid X receptor (RXR).[4-5, 7-8]
  - Six major subtypes of receptor have been identified, which are encoded by separate genes (RARα, -β, -γ, and RXRα, -β, -γ).
- The RXRγ isoform is undetectable in normal thyroid and variably expressed in malignant tumors, and this receptor predicts response to retinoid treatment in cell lines.[2]
  - A phase II trial with the retinoid bexarotene was stopped prematurely due to toxicity and low efficacy.[6]

GOAL OF THE STUDY

Hypothesis

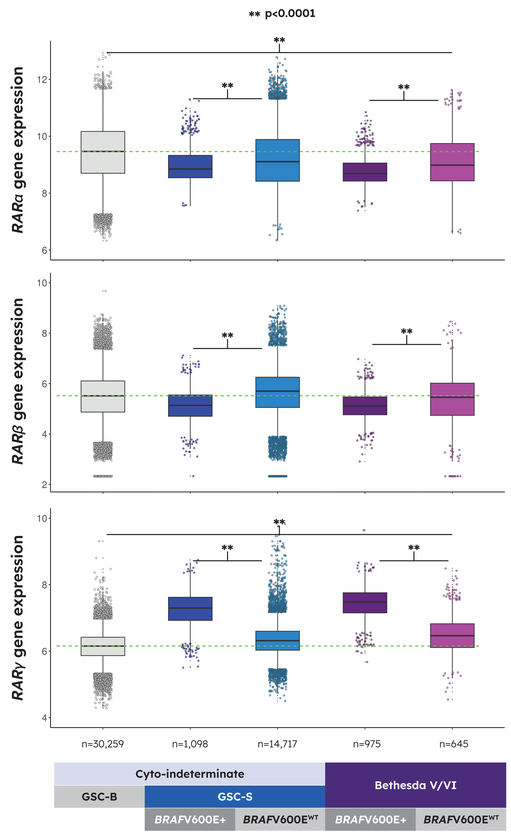
Retinoid receptors will be differentially expressed in thyroid tumors based on (B)ethesda cytology category, Afirma GSC result, and mutational status.

METHODS

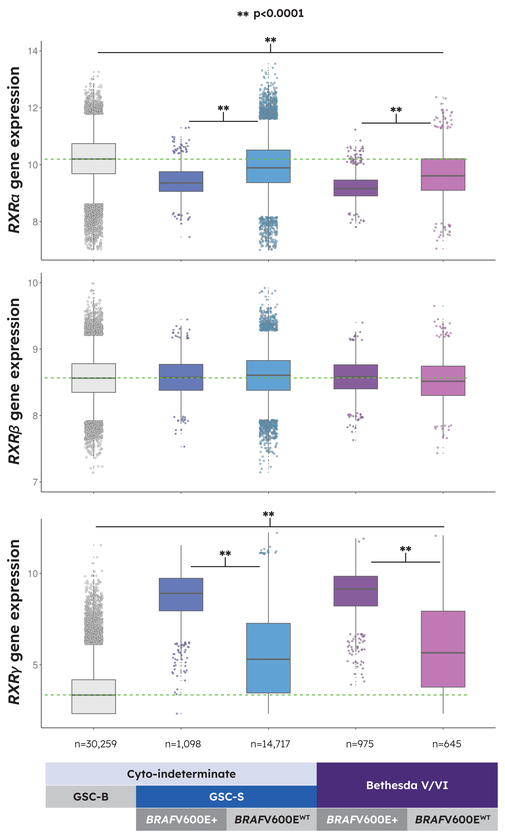
- mRNA expression of the six retinoic acid (RAR) and retinoid X receptor (RXR) isoforms was analyzed across thyroid nodules sent for Afirma testing.
- Differential expression was explored across a cohort of nodules with BIII/IV cytology and Afirma benign (GSC-B) or suspicious (GSC-S) categories, BV/VI nodules, and relative to *BRAF*V600E status.
- Another cohort with *TERT* promoter mutational status was analyzed along with expressed variant and fusion alterations as well as other genomic markers of tumor aggressiveness.

RESULTS

- RARα
  - Lower expression in BV/VI vs GSC-B
- RARβ
  - Lower expression in *BRAF*V600E+ tumors
- RARγ
  - Higher mRNA expression in GSC-S and BV/VI
  - Highest expression in *BRAF*V600E+ tumors

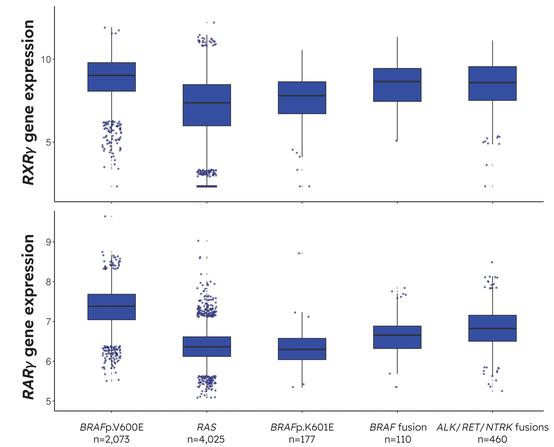


- RXRα
  - Lower expression in GSC-S and Bethesda V/VI samples
  - Lower expression in samples with *BRAF*V600E mutation
- RXRβ
  - No differences in expression
- RXRγ
  - Higher expression in GSC-S and BV/VI versus GSC-B
  - Highest expression in *BRAF*V600E+ tumors



RARγ and RXRγ vs. other alterations in GSC-S & BV/VI

Expression of RARγ and RXRγ is higher in samples with *BRAF*p.V600E compared to other alterations (p< 0.001 for all)



CONCLUSION

- RARγ and RXRγ appear to be coordinately expressed based on cytology, Afirma GSC and mutation status.
- RARγ and RXRγ expression may be driven by MAPK signaling.
- RARγ and RXRγ may be good therapeutic targets in advanced thyroid cancer.
- Future studies should evaluate the underlying mechanism of how *BRAF*V600E and MAPK signaling may affect RARγ and RXRγ expression.

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