Endocrine Surgery Review

Integrative analysis of genomic and transcriptomic characteristics associated with progression of aggressive thyroid cancer

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In Brief

In the United States, population based studies suggest increased incidence along with incidence-based mortality for thyroid cancer (TC) overall and specifically for advanced-stage papillary thyroid cancer.(1) Unlike early stage well differentiated thyroid malignancy, anaplastic and advanced differentiated TC are both associated with poor survival.(1, 2) Therefore, studying mechanisms of carcinogenesis by molecular profiling of these neoplasms is critical to better understand tumor behavior and enhance existing diagnostic and therapeutic options. Several studies have identified mutational involvement of multiple oncogenes and tumor suppressor genes (TSGs) in the development and progression of anaplastic and advanced differentiated TC, including but not limited to BRAF, RAS and TERT mutations.(3) The rapid evolvement of knowledge of the genetic pathogenesis of TC has a significant clinical impact as highlighted by the incorporation of BRAFV600E mutation into the 2015 American Thyroid Association risk stratification system for persistent/recurrent papillary thyroid cancer and also by the increased utilization of targeted kinase inhibitor therapy.(4) While the molecular profiles of differentiated thyroid cancer have been extensively studied, the underlying mechanisms of progression to anaplastic or advanced differentiated TC are not well characterized.

In this study, Yoo and colleagues aimed to study the genomic and transcriptome characteristics of advanced differentiated thyroid cancer (ADTC) and anaplastic thyroid cancer (ATC) using massively parallel DNA and RNA sequencing methods and epigenetic profiling by Enhancer prediction and DNA methylation analysis. (5) Specimens were obtained for analysis from patients undergoing thyroidectomy for primary, distant metastatic, locally recurrent or residual disease and included a total of 113 advanced TCs: 27 ATCs, 15 poorly differentiated TCs (PDTCs), 28 focal ATC/PDTCs, 12 widely invasive follicular TCs (wiFTCs), and 31 metastatic papillary TCs (PTCs). Whole and targeted sequencing were performed on 13 ATCs and 3 focal ATC/PDTCs with concordance rate around 92% between both methods.

Mutational landscape: Overall, the tumor mutational burden was significantly higher in ATC than in other types of thyroid cancer. BRAF V600E and RAS were identified as major driver genes in ATC as each mutation was detected in about 40% of ATC and 27% of PDTC. Over 80% of focal ATC/PDTCs and 64% of metastatic PTC had BRAF V600E mutation. On the other hand, RAS mutation was present in 67% and 23% of wiFTC and metastatic PTC, respectively. Along with the main driver genes, BRAF V600E and RAS, the authors identified multiple co-mutated genes in ATC and ADTC including: TERT, AKT1, PIK3CA, and EIF1AX. AKT1/PIK3CA and EIF1AX were frequently co-mutated in ATCs and were associated with more aggressive neoplasm behavior. TERT was the most frequently co-mutated gene in ATC as it was detected in in over half of cases and was also detected in advanced DTCs

specifically within wiFTC as it was present in over 90% of wiFTC while other mutations were rarely detected in this subtype. In contrast to differentiated thyroid cancer where TSG alterations are not very common, TSGs were frequently detected in ATCs (over 70%) and ADTCs (around 20%) with TP53 being the most commonly altered gene.

Somatic TERT rearrangements in wiFTC: In addition to promoter mutation, two structural rearrangements within or adjacent to TERT were found in wiFTC. The authors identified a TERT fusion gene, PDE8B-TERT, which was not previously described in thyroid cancer. Interestingly, promoter mutations inducing TERT expression were higher in ATC than in DTC.

Prognostic significance of CDKN2A loss for disease-specific mortality: In addition to TP53, CDKN2A was detected in ATC and in ADTCs. According to this study, CDKN2A loss was associated with lower differentiation scores and increased disease-specific mortality in ATC and ADTC after adjusting for clinically relevant factors (age, sex, distant metastasis, and tumor origin), which may suggest it can represent a prognostic factor.

In addition to the three previously identified molecular subtypes of thyroid cancer: BRAF V600E-like, RAS-like, and Non-BRAF non-RAS (NBNR), transcriptome analysis in the current study revealed a fourth type: ATC-like, which hardly shows the molecular distinctions resulting from the types of driver mutations that have been shown in DTC.

Potential druggable targets in ATC: The authors studied different pathways involved in the progression of thyroid cancer: the VEGF- and the Notch-signaling pathways which were significantly elevated in BRAF V600E-positive ATC and the MAPK- and the JAK-STAT-signaling pathways which were elevated in RAS-positive ATC. To further evaluate the role of these pathways as potential druggable targets, the authors performed functional *in vitro* experiments with ATC cell lines, which showed decreased cellular proliferation upon targeting JAK-STAT pathway with ruxolitinib in RAS-positive ATC. On the other hand, no effects were detected upon inhibiting the VEGF-Notch signaling in BRAF V600E positive ATC.

Critique

The authors applied high-throughput massively parallel DNA and RNA sequencing methods on different types of human thyroid cancer tissues to further delineate the genomic and transcriptome characteristics of advanced TC. The study findings help to expand the current knowledge about the role of different genetic mutational spectra as well as the role of potentially targetable biological pathways in TC development and progression. Moreover, based on these results, a new thyroid cancer subtype was identified: ATC-like. However, this study has some limitations. Various sequencing methods were performed including WGS, WES and targeted sequencing which can prone the results to bias as these methods have different characteristics specifically different sequencing range and depth. In addition, matched normal and tumor DNA analysis was not performed for the targeted sequencing which can also introduce bias to the results.

Future Directions

These study findings provide more tailored diagnostic and therapeutic interventions and deeper understanding of different genetic mutations involvement in aggressive TC types. These results can be further used to perform in depth genetic functional validation studies for better understanding of neoplasm progression and its underlining mechanisms. The role of described activated molecular pathways and potential effect of targeted therapy needs to be further investigated and expanded.

References

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