The transformation from thyroid papillary carcinoma to anaplastic carcinoma point of view

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Papillary thyroid carcinoma (PTC) is the most common type of thyroid neoplasm and generally well-behaved with favorable survival rates. However, a small subset of these well-differentiated tumors can unfortunately transform into anaplastic thyroid carcinoma (ATC) with highly aggressive behavior and dismal prognosis (1-4). As widespread adoption of next generation sequencing (NGS), a number of molecular alterations involved in this transition had been delineated. Previous studies supported the hypothesis that ATC might arise from dedifferentiation of preexisting PTC tumor stepwise (2,5,6). In consideration of their totally different outcomes, it is of utmost importance to recognize the rare aggressive PTC. In addition, more precise sub-classification and prognostic evaluation system of thyroid carcinoma need be established.

Much progress has been made in uncovering molecular alterations that were responsible for thyroid carcinogenesis and progression (5-8). Comprehensive molecular studies have shed lights on several genetic mutations or chromosomal abnormalities in both ATC and PTC based on NGS techniques (9-11). By comparing with their genome characteristics, mRNA and protein expressions, the results showed greatly overlapping between ATCs and PTCs (5,6,12). However, in spite of the homogeneity, ATCs present impaired gene regulations according to cell cycle control and proliferation rate (5,6). A number of genetic alterations have been investigated to play a role in anaplastic transformation, including derangement of the E-cadherin/catenin complex, additional mutation of TP53, bcl-2, cyclin D1, β-catenin, c-myc and genetic alterations in *BRAF*, *RAS* and *PIK3CA* genes (1,3,10). To date, the timing or sequence of the genetic alterations that occur during PTC progression is still obscure. Some previous studies described *BRAF* and *PI3KCA* mutation as beneficial events for ATC formation, and *TERT* promotor mutation was not involved (2,10,13,14). In another research, by studying concomitant ATC and PTC samples, *BRAF* and *PI3KCA* mutations were found more prevalent than in *de novo* ATC (8).

In order to uncover the risk factors for anaplasia transformation, Oishi *et al.* investigated genetic alterations of PTC and ATC components in 27 tumors in which anaplastic carcinoma coexisted with antecedent papillary carcinoma. In accordance with many other studies (10,13), Oishi *et al.* present that expression of p53, loss of TTF-1 and SWI/SNF mutations are associated with transforming to ATC, which might be late events for tumor progression (15). Besides, the present study holds quite a different view about the role of *TERT* promotor mutation. The researchers demonstrate that PTCs harboring *TERT* promotor mutation have aggressive behaviors and are more likely to transform into ATC (15). It's the first time to place *TERT* mutation as a high risk for anaplastic formation.

Clinicians are badly in need of a reliable biomarker to predict prognosis and offer intervention at early stage for those aggressive PTC patients. *BRAF* mutation, as the most common genetic alteration in PTCs, is existing in more than 60% PTCs and also prevalent in ATCs (4,9). Although it has a high specificity for thyroid cancer, the diagnostic and prognostic value is still controversial (9,16).

TERT promotor has a much lower mutation detection rate than *BRAF*, reported about 9% (9). But it has been well documented as an aggressive clinicopathological characteristic for thyroid cancer (4,9,12,17-19). Current reports have established a vital role of TERT promoter mutation in the tumorigenesis of human thyroid carcinoma (16,17,20). Combined with this finding, the prognostic value of *TERT* promotor mutation will be of more clinical significance. It is not only indicative of aggressive behavior but also a risky factor of anaplasia transformation. In this way, detecting the mutation status of *TERT* promoter has the potential to enable treatment personalization and monitoring across the course of the disease for those particular PTC patients.

The present work truly presents an inspiring finding; however, sample selection bias and studying retrospectively may reduce its reliability and limit its application in clinic. As many other studies preciously demonstrated that BRAF mutation was associated with anaplasia transformation (2,10,13,14), and *TERT* mutations frequently occurred together with BRAFV600E mutations (20), combined detecting of TERT with *BRAF* mutation may be more significant and complementary. Besides, more multicenter large-scale clinic trails including comprehensive tumor samples are wanted.

Overall, although controversial, the study by Oishi *et al.* presents a challenging result that PTCs with *TERT* promotor mutation have aggressive behaviors and are more likely to transform into ATCs. This research illustrates a promising biomarker and will inspire more researchers applying themselves to uncover profound mechanism in thyroid carcinogenesis.

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Footnote

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