Identifying Genetic Alterations in Poorly Differentiated Thyroid Cancer: A Rewarding Pursuit

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The concept of “poorly differentiated thyroid carcinoma” (PDTC) was initially proposed more than 25 yr ago (1, 2). It described a subgroup of thyroid carcinomas that seemed to fall, in terms of clinicopathological behaviors and aggressiveness, between the classically defined differentiated papillary thyroid carcinomas (PTC)/follicular thyroid carcinomas (FTC) and the undifferentiated anaplastic thyroid carcinomas (ATC). Over the next 20 yr of research, numerous studies supported the existence of such a clinicopathological entity of thyroid carcinoma, leading to the official inclusion of PDTC as a separate tumor entity in the World Health Organization (WHO) classification of thyroid tumors several years ago (3).

In recent years, much effort has been made to identify genetic alterations in PDTC. Most of the studies have been focused particularly on identifying genetic alterations in the MAPK and phosphatidylinositol 3-kinase (PI3K)/Akt pathways, two major signaling pathways that have been extensively studied for their fundamental roles in thyroid tumorigenesis (4, 5). Examples of these genetic alterations include the \( \text{BRAF} \) mutation and \( \text{RET/PTC} \) rearrangements in the former pathway and \( \text{Ras} \) mutations in the latter pathway. Less studied genetic alterations include \( \text{PAX8/PPAR} \) rearrangement, \( \beta \)-catenin mutation, and a few others. A somewhat disturbing issue regarding the actual role of these genetic alterations in PDTC is the large variation of their prevalences and types in PDTC reported by different investigators. A possible reason for this is that, unlike PTC, FTC, and ATC, the diagnostic criteria used for PDTC varied considerably among different investigators. This may not be surprising because PDTC or PDTC-like tumors may display an intermediate spectrum of clinicopathological behaviors between differentiated and undifferentiated thyroid carcinomas. It is often, therefore, not a straightforward task to clearly define PDTC based on clinicopathological grounds, particularly when the classical WHO criteria are not uniformly followed. It is also likely that PDTC can derive from different differentiated thyroid carcinomas that usually harbor different genetic alterations, resulting in considerable diversity of genetic patterns in PDTC.

A good example to illustrate this is that \( \text{BRAF} \) mutation is most commonly seen in conventional and tall cell PTC (6), whereas \( \text{Ras} \) mutation is most commonly seen in follicular variant PTC (7) and FTC (8). If PDTC can derive from all these thyroid carcinomas, significant genetic heterogeneity may be expected in this cancer when analyzed as a whole.

In this issue of \( \text{JCEM} \), Volante et al. (9) conducted a comprehensive analysis of several major genetic alterations, including \( \text{N-Ras} \), \( \text{K-Ras} \), \( \text{H-Ras} \), and \( \text{BRAF} \) mutations and \( \text{RET/PTC1} \) and -3 and \( \text{PAX8/PPAR} \) rearrangements in a large series of PDTC. An important and unique aspect of this study is that the authors strictly used the WHO classification criteria that were recently refined by the Turin conference (10). A large panel of world experts at this Turin conference proposed a diagnostic algorithm based on the interpretation of the WHO criteria and offered a uniform consensus approach for classification of PDTC. Thus, in the Volante et al. study (9), the criterion used for PDTC is the version currently agreed upon among authoritative world experts, making the selection of PDTC cases more uniform and tumors pathologically more homogenous than previous studies. With this careful selection of PDTC, the authors demonstrated that \( \text{N-Ras} \) codon 61 mutation was the predominant genetic alteration among all the genetic alterations examined. To ensure the accuracy of genetic testing, alternative
methods were used for the analysis of some of the genetic alterations. This was therefore a carefully designed and well-conducted study. Taking a further step from showing the predominance of Ras mutation in PDTC, the authors also interestingly and for the first time showed a significant association of N-Ras mutation with decreased survival of the patients with PDTC. These data thus provide strong evidence that Ras mutation plays an important role in the tumorigenesis of PDTC. Several previous studies reported a high prevalence of Ras mutations in PDTC and showed their association with aggressive pathological outcomes of thyroid carcinomas (11–14). The diagnostic criteria for PDTC used in these studies, however, did not seem to be as clear and uniform as in the Volante et al. study (9). This might explain the high prevalence of K-Ras mutation in some of these studies (13, 14) as opposed to a high prevalence of N-Ras mutation in the Volante et al. study (9). N-Ras mutation has been widely shown to be the most common Ras mutation in thyroid cancers (8). This is consistent with the conclusions of the Volante et al. (9) study on the important role of Ras mutations in PDTC. Because this well-designed Volante et al. study showed very rare or absent BRAF mutation and RET/PTC and PAX8/PPARγ rearrangements in PDTC, these genetic alterations do not seem to play a major role in PDTC. With respect to BRAF mutation, PDTC is apparently different than ATC because the latter harbored the mutation in about 25% of the cases (6).

A fundamental question regarding the tumorigenesis of PDTC concerns how this cancer has developed. Does it originate from PTC and FTC or occur de novo? The Volante et al. study provided interesting implications in this regard (9). The genetic patterns of PDTC reported in the Volante et al. study are consistent with the notion that some PDTC derives from follicular variant PTC or FTC because the latter two thyroid carcinomas most commonly harbor N-Ras mutations (7, 8). This possibility is consistent with the finding of Volante et al. that Ras mutation was present in PDTC either with or without PTC components. This is also consistent with the notion that such PDTC could further progress into ATC because the latter commonly harbors N-Ras mutations (15, 16). The progression from PDTC to ATC most likely requires additional genetic alterations because Ras mutations commonly coexist with other genetic alterations in ATC (15, 16). Because only PDTC with coexisting PTC components harbored BRAF mutation as shown in the Volante et al. study (9), this type of PDTC could be a precursor of BRAF mutation-positive ATC since the latter harbored BRAF mutation usually when coexisting with PTC components as shown in many studies (6). There is also other evidence supporting the notion that differentiated thyroid cancer can progress into PDTC and subsequently to ATC (17). PDTC could also possibly develop de novo without PTC or FTC precursors. Either way, N-Ras mutation seems to play an important role in the tumorigenesis and tumor progression of PDTC as suggested by its association with a poor clinical course of PDTC demonstrated in the Volante et al. study (9). Whether N-Ras mutation can itself initiate the development of PDTC remains to be determined. It is probably more likely that coexisting genetic alterations that are yet to be identified synergize N-Ras mutation in the promotion of PDTC tumorigenesis and progression because N-Ras mutation alone can actually occur in benign follicular thyroid adenoma and differentiated FTC in which, unlike in PDTC, it does not seem to confer the tumor-increased aggressiveness (8).

Although N-Ras mutation was the predominant genetic alteration in PDTC found in the Volante et al. (9) study, the majority of PDTC did not harbor any of the genetic alterations examined in this study. Therefore, the genetic background for most cases of PDTC still remains to be defined. It would be particularly interesting to see whether various genetic alterations in the PI3K/Akt pathway, which are extremely common in ATC (16), also occur in PDTC. These may include PTEN mutation, PIK3CA mutation and amplification, and various receptor tyrosine kinase gene amplifications (16). This is particularly possible given the important role of aberrant activation of the PI3K/Akt pathway driven by these genetic alterations in the progression from differentiated to undifferentiated thyroid tumors (15).

PDTC is well known for its clinicopathological aggressiveness and high mortality. There has been no known molecular marker that can predict the clinical course of this cancer. The Volante et al. study for the first time provided such a molecular marker, N-Ras mutation, that can predict a significantly decreased survival rate of patients with PDTC. Thus, Ras mutation analysis in PDTC has potentially a clinical place in assisting risk stratification of PDTC patients to identify those who may need more aggressive treatments. This is similar to the clinical value of BRAF mutation as a prognostic molecular marker in PTC (18). Numerous studies have demonstrated that BRAF mutation is associated with aggressive pathological characteristics of PTC and predicts recurrence of this cancer. A recent study also demonstrated association of BRAF mutation with a decreased survival rate of PTC patients (19). If the predictive value of Ras mutation for poorer survival of PDTC patients demonstrated in the Volante et al. study (9) can be generally confirmed in future studies, this genetic marker, like BRAF mutation in PTC, will likely have an important impact on the clinical management of PDTC. It is interesting that Ras mutation is associated
with a poorer clinical outcome in PDTC but not in differentiated thyroid cancer. In fact, compared with BRAF mutation, Ras mutation was associated with less aggressive clinicopathological outcomes and molecular derangements in PTC (18). As discussed above, it remains to be investigated whether additional coexisting genetic alterations exist that can synergize the aggressive role of Ras mutations in PDTC. This may be similar to the case of PIK3CA amplification that was shown to be associated with increased aggressiveness of PTC only when coexisting with BRAF mutation (20).

The demonstration of the importance of Ras mutations in the aggressiveness of PDTC also provides a potentially effective molecular target for the development of novel therapies for the subgroup of PDTC harboring this mutation. Because Ras mutation in thyroid cancer may predominantly activate the PI3K/Akt pathway over the MAPK pathway, targeting the PI3K/Akt pathway at steps downstream of Ras, such as Akt or mammalian target of rapamycin, may be effective for PDTC harboring Ras mutations. Genetic-targeted therapy has become increasingly recognized as a unique therapeutic strategy for human cancer. It was recently demonstrated that genetic alterations in the PI3K/Akt pathway, including Ras mutations, conferred thyroid cancer cells sensitivity to Akt and mammalian target of rapamycin inhibitors (21), supporting genetic-targeted therapeutic approaches for thyroid cancer as discussed recently (22). This remains as an attractive therapeutic strategy to be specifically tested for PDTC.

The work of Volante et al. (9) has set a good example in defining genetic alterations in PDTC by carefully and accurately using recently refined diagnostic criteria. The identification of Ras mutation as a predominant genetic alteration and demonstration of its predictive role for a poorer clinical course of PDTC have important biological and clinical implications for this cancer. Effective management of PDTC, an often incurable cancer, needs novel and accurate diagnostic, prognostic, and therapeutic strategies, which will in turn rely on identification of novel molecular mechanisms, particularly genetic alterations, in this cancer. Although the recently refined Turin criteria for PDTC will facilitate accurate classification and diagnosis of PDTC as seen in the Volante et al. study, diagnostic uncertainty for PDTC is still likely to occur given the often heterogeneous clinicopathological characteristics of this cancer entity. It is therefore tempting to speculate that specific genetic markers and their combination patterns may help to more accurately classify and define the entity of PDTC. Perhaps use of certain genetic markers in combination with clinicopathological criteria may provide an even better approach to defining and classifying PDTC. Although the currently known genetic information for PDTC is limited, it is expected that, like ATC, extensive genetic alterations in multiple signaling pathways, such as the MAPK and PI3K/Akt pathways, are present in PDTC. Epigenetic alterations, such as aberrant gene methylation as seen in other types of thyroid cancer (23), may also exist in PDTC. Identification of these genetic alterations and characterization of their clinicopathological relevance may significantly impact the management of PDTC. This is a challenging yet rewarding task to pursue.

Acknowledgments

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This work was supported by National Institutes of Health Grant ROI-CA134225-01 (to M.M.X.).

Disclosure Summary: The author has nothing to disclose.

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