New genomic somatic amplifications and deletions in papillary thyroid cancer

Myriem Boufraqueh¹ · Electron Kebebew¹

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There have been striking changes in the epidemiology of thyroid cancer worldwide with higher incidence rates, with low-risk or clinically less significant papillary thyroid cancer accounting for more than 80 % of new cases each year [1, 2]. During this change in epidemiology, our knowledge in the genetic and genomic alterations associated with thyroid cancer initiation and or progression has also expanded tremendously [3]. As precision medicine is becoming a reality for some solid malignancies, the application of new knowledge to the management of thyroid cancer is going to be imperative to precisely treat patients based on the genetics/genomics of their tumor, especially when it is found to be associated with disease behavior [4].

The study by Passon and colleagues from Italy reports new findings based on a careful analysis of 27 papillary thyroid cancer samples using high-resolution comparative genomic hybridization [5]. The investigators found that genomic amplifications were higher in high/intermediate-risk group tumors and that genomic deletions were higher in low-risk tumors based on the American Thyroid Association (ATA) risk stratification system. Several of these genomic amplifications and deletions were recurrent (occurred in more than 20 % of tumor samples) and several of the genes in the chromosomal loci with deletions have been implicated to be involved in thyroid cancer or their expression is dysregulated in cancer. The most frequent amplifications that were detected in 2q35, 4q26, and 4q34.1 contained *FNI*, *PDE5A*, and *GALNTL6*, respectively. The

2q35 locus is thought to be a breast cancer susceptibility locus, and *FNI* expression was found to be restricted to thyroid cancer samples and absent in benign lesions [6, 7]. Interestingly, 60 % of the cases with 2q35 amplification were TNM Stage I according to the American Joint Committee on Cancer (AJCC) staging system, whereas more than 70 % were considered intermediate/high risk according to the ATA risk classification system. Although both systems include some of the same variables, the AJCC staging system also includes the patient's age at diagnosis so that patients younger than 45 years even with lymph node and or distant metastases are considered as having only stage I/II disease. Also the ATA risk stratification system includes postoperative serum thyroglobulin level measurement. Thus, these factors likely explain the somewhat discrepant results. The amplification in 4q26 involving *PDE5* was more prevalent in intermediate/high-risk cancers. Interestingly, studies have shown that tumors with high expression level of *PDE5* have lower mRNA expression of differentiation markers or thyroid-specific genes (*TG*, *TSHR*, *TPO*, and *NIS*) [8]. Thus, *PDE5* could be involved in thyroid cancer initiation, progression, or even radioiodine resistance. The authors also investigated the *BRAF* mutation status in the tumors analyzed but found no significant association with genomic amplifications or deletions. Most, but not all, studies have suggested that papillary thyroid cancers with *BRAF* mutations are more aggressive and that it is one of the most frequent genetic alterations in papillary thyroid cancer [3, 9]. Passon and colleague did find that 8 of the *BRAF* V600E mutant samples were in patients with ATA intermediate-risk papillary thyroid cancers. It would be interesting to know if the genomic deletion status in addition to *BRAF* mutation status could better stratify ATA low-risk from intermediate/high-risk papillary thyroid cancer or even outperform

✉ Electron Kebebew
kebebewe@mail.nih.gov

¹ National Cancer Institute, National Institutes of Health,
Bethesda, MD, USA

the currently used staging or risk classification systems for thyroid cancer with respect to the risk of persistent/recurrent disease. While the study by Passon and associates is an initial investigation, such findings could be used as adjunct prognostic markers that could be translated into making therapeutic decisions if they are validated to be predictors of patient outcome similar to the use of *MYCN* amplifications in neuroblastoma [10].

In conclusion, we congratulate Passon and colleagues on their report of new, recurrent chromosomal abnormalities in papillary thyroid cancer which may have important roles in thyroid carcinogenesis and could translate to prognostic markers that can be used to make patient care decisions.

Compliance with ethical standards

Conflict of Interest The authors have no conflict of interest to report.

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