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Expression of Glucagon-Like Peptide-1 Receptor in Papillary Thyroid Carcinoma and Its Clinicopathologic Significance
(*Endocrinol Metab* 2014;29:536-44, Min Jung Jung et al.)

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Thank you for your interest and comments on our article entitled "Expression of glucagon-like peptide-1 receptor in papillary thyroid carcinoma and its clinicopathologic significance," which was published in *Endocrinology and Metabolism* [1].

We reported the expression of the glucagon-like peptide-1 receptor (GLP-1R) in papillary thyroid carcinoma (PTC) tissues based on immunohistochemical (IHC) staining. However, we could not find a meaningful relationship between clinical prognostic markers and GLP-1R expression in PTC, but the less multifocality of GLP-1R expression in PTC tissues. These findings were unexpected and interesting because previous studies reported that GLP-1R is not expressed in thyroid follicular cells and GLP-1 plays a possible role in cell proliferation and apoptosis in pancreatic β-cells.

IHC staining is well-established and used widely for identifying specific pathological processes, including protein expression nevertheless, the pathologist's interpretation is subjective. To convert the subjective perception of IHC marker expression into quantitative data, various semiquantitative scoring systems have been suggested. For example, in breast cancer, representative tumors were subjected to several IHC stains, including estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67. Pathologists use the quickscore, modified H-score, immunoreactive score and Allred score [2,3] as generally accepted standard interpretation guidelines for IHC staining of ER and PR. In Allred score, pathologists score the proportions of ER-positive immunoreactive cells into six categories (0, no cells are ER-positive; 1, ≤1%; 2, 1% to 10%; 3, 11% to 33%; 4, 34% to 66%; and 5, 67% to 100% are ER-positive) and intensity into four categories (0, negative; 1, weak; 2, intermediate; and 3, strong). The final score is the sum of these two scores, where the minimal standard hormone receptor-positive score is 3 and the mandatory minimum of tumor cells is 1% regardless of intensity. A similar approach was demonstrated in "quickscore," modified H-score system, with the differences in values in proportion category A from 1 to 6 (1, 0% to 4%; 2, 5% to 9%; 3, 20% to 39%; 4, 40% to 59%; 5, 60% to 79%; and 6, 80% to 100%) and using multiplication for final scoring [2]. However, the generally accepted interpretation guideline for IHC staining of HER2 is different. Pathologists evaluate the immunoreactive pattern (complete vs. incomplete circumferential membrane staining), intensity (none,

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weak, moderate, and intense), and proportion of immunoreactive cells (≤10%, >10%). The final interpretation is based on the combination of these three results [4]. In the general guideline for interpreting the IHC staining for Ki67, pathologists evaluate only the proportion of immunoreactive cells (low, Ki67 index <14%; high, Ki67 index ≥14%) [5]. Furthermore, investigators have used various interpretation methods to compensate for the equivocal immunoreactivity with many IHC stains [6]. Even among researchers using quickscore, there are various interpretation methods and criteria based on the proportion and intensity scores, calculation method (addition vs. multiplication), and what is interpreted as a positive immunoreaction. These differences in the IHC interpretation system are considered a major cause of discordant results among studies.

In our study, we interpreted the results of IHC staining using both intensity and the proportion of GLP-1R immunoreactive cells. Negative immunoreactivity was defined as no staining or ambiguous staining and strong immunoreactivity was defined as any cells with strong staining intensity regardless of the distribution. However, weak intensity was interpreted according to the distribution of immunoreactive cells in the entire tumor with a minimum cutoff value of 5%. This interpretation system focuses more on the intensity of stained cells compared to the breast tumor quickscore, in which the proportion of stained cells is more important. Our study is pioneering research on GLP-1R expression in PTC based on IHC expression. Therefore, we focused on the existence of aberrant GLP-1R expression in PTC, rather than the differences between expressed or non-expressed GLP1-R in PTC or differences among various degrees of GLP-1R expressed in PTC. Moreover, the distribution of GLP-1R immunoreactive cells was diffuse and spread over 50% of the entire tumor in all except two of 18 cases, which showed moderately intense immunoreactivity in 20% of the tumor. Therefore, fine separation of immunoreactive cell proportion is considered as less meaningful. To date, there is insufficient information to determine the best interpretation method for GLP-1R expression in PTC. We hope to obtain more objective and validated results in future studies including a more quantitative scoring system for IHC staining, such as the quickscore method. We sincerely appreciate Park et al. for their interest in our study and knowledgeable comments.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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