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Measuring a Three-Gene Panel May Distinguish Malignant from Benign FNA Samples

Prasad NB, Kowalski J, Tsai HL, Talbot K, Somervell H, Kouniavsky G, Wang Y, Dackiw AP, Westra WH, Clark DP, Libutti SK, Umbricht CB, Zeiger MA. Three-gene molecular diagnostic model for thyroid cancer. Thyroid. 2012;22:275-84. Epub January 26, 2012.

SUMMARY

Background

Fine-needle aspiration (FNA) biopsy of thyroid nodules results in an indeterminate or suspicious diagnosis in one fourth of biopsies. This often leads to surgical thyroidectomy in patients who have benign nodules. To improve the diagnosis of thyroid cancer, one approach has been to measure molecular markers that are highly expressed in thyroid cancers in comparison with benign nodules. By microarray analysis of benign and malignant thyroid tumors, these authors had previously identified 75 genes that were differentially expressed. This study determined that measurement of three unique genes resulted in good diagnostic discrimination of benign from malignant nodules.

Methods

A set of 95 intraoperative FNA specimens was collected for molecular analysis and the results were correlated with the permanent histology. RNA was extracted from the samples and subjected to quantitative RT-PCR for analysis of 10 genes that previous work had shown to be promising candidates. Of the 95 samples, 27 had corresponding indeterminate or suspicious preoperative cytology. Each marker was examined separately and in combination by univariate and multivariable analysis to determine odds ratios and 95% confidence intervals of various models. The proteins expressed by these same genes were examined by immunohistochemistry in separate studies on material obtained from paraffin blocks.

Results

The FNA samples were obtained from the following histologic lesions: 50 adenomatoid nodules, 10 follicular adenomas, 5 Hürthle-cell adenomas, 23 papillary thyroid carcinomas, 5 follicular variant of papillary thyroid carcinomas, 1 lymphocytic thyroiditis nodule, and 1 Graves' disease.

In the FNA samples, all 10 genes showed significantly higher odds of being associated with malignancy as compared with benign lesions; the gene, MRC2 (mannose receptor, C type 2) showed the highest discriminating ability. The combination of 3 genes—MRC2+HMGA2 (high mobility group AT-hook 2)+SFN (stratifin)—had a sensitivity of 71%, specificity of 84%, positive predictive value (PPV) of 65%, and negative predictive value (NPV) of 88%. Of the 27 samples that had suspicious or indeterminate FNA results preoperatively, the 3-gene model was 96% specific and 60% sensitive in the prediction of malignancy (PPV, 75%; NPV, 91%). The results of the immunohistochemistry were similar to the PCR data for these 3 genes.

Conclusions

The results suggest that a 3-gene model for the molecular diagnosis of indeterminate thyroid nodules is feasible and promising and that implementation of this as an adjunct to thyroid cytology may significantly impact the clinical management of patients with suspicious or indeterminate thyroid FNA nodules.

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ANALYSIS AND COMMENTARY

Although a great deal of work went into this study by a very prolific group, the results must still be regarded as preliminary. There were no follicular carcinomas in the FNA group, although there were some follicular and Hürthle-cell carcinomas in the immunohistochemistry group. Since there were no follicular cancers in the FNA samples, the three-gene classifier (MRC2+HMGA2+SFN) is not established for distinguishing follicular adenoma from carcinoma. As the authors state, the method must now be validated by applying it to a test set of samples. A different three-gene biomarker panel was thought to be useful for diagnosis of thyroid cancer, but its diagnostic accuracy was low in a subsequent study (1).

The efficacy of this study must be compared with that of the miRNA studies described in the previous article in this issue (2) and with the use of the more established thyroid cancer biomarkers, BRAF, RET/PTC, RAS, and PAX8/PPARg (3). These biomarkers represent mutations that are understood well with regard to activating pathways of growth. In contrast, the genes up-regulated in the current study do not have well-established roles in oncogenesis, but certainly have potential for contributing to neoplastic growth.

MRC2 is a recycling endocytic receptor that functions in cell motility and remodeling of the extracellular matrix by promoting cell migration and uptake of collagens for intracellular degradation. HMG proteins function as architectural factors and are essential components of the enhancesome. The protein contains structural DNA-binding domains and may act as a transcriptional regulating factor. SFN is an adapter protein that binds to a large number of partners implicated in the regulation of a large spectrum of both general and specialized signaling pathways. I look forward to reading the study that validates these genes as accurate biomarkers for thyroid cancer when applied to FNA in the clinical setting.

— Jerome M. Hershman, MD

References

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