17. DIAGNOSTIC MOLECULAR MARKERS IN THYROID CANCER

MATTHEW D. RINGEL, M.D.

Associate Professor of Medicine Department of Medicine, Divisions of Endocrinology and Oncology The Ohio State University, Columbus, Ohio

INTRODUCTION

Thyroid cancer is the commonest classical endocrine tumor, accounting for approximately 1% of all cancers. The diagnosis of thyroid cancer is typically made on cytopathologic features on fine needle aspiration or histological features on surgical samples. Following treatment of patients with thyroidectomy, and in some cases radioiodine, patients are monitored for disease recurrence using a variety of scanning modalities and serum thyroglobulin. The accuracy of both the preoperative testing and postoperative monitoring is excellent in many cases; however, there are some important deficiencies that have led to the development new tools for clinical use. Specifically, the application of molecular methods to the analysis of pathology and blood samples has led to the development of highly sensitive markers for the diagnosis of new cases of thyroid cancer, and in the evaluation of patients for recurrent disease. In this review, the molecular analysis of thyroid nodules, lymph nodes and peripheral blood as adjunctive tests for thyroid cancer will be discussed.

PREOPERATIVE EVALUATION OF THYROID NODULES

Thyroid nodules are extremely common with prevalence rates approaching 50–60% of adults under 60 years old. Because only approximately 5% of thyroid nodules are malignant, accurate pre-operative characterization of thyroid nodules is critical in selecting patients appropriate for surgical thyroidectomy. Fine needle aspiration (FNA) is the single most important diagnostic procedure in the evaluation of thyroid nodules.

Table 1. Molecular markers for thyroid nodules and lymph nodes

Potential diagnostic markers for thyroid nodules and lymph nodes	
Telomerase	GLUT-1
Galectin-3	CA 19-9
Thyroid peroxidase	CD 15
Thyroglobulin	HBME-1
Oncofetal fibronectin	CD 30
ret/PTC oncogenes	CD 57
Pax8/PPARγ oncogene	CD 97
B-Raf mutations	Leu-7
Nm23	Epithelial Membrane Antigen
High mobility Group I (Y) Protein	Cyclooxygenase 2
Ceruloplasmin	Cytokeratin 19
Survivin	Cytokeratin 20
	TSH Receptor Hypermethylation

For small, solid nodules, experienced cytopathologists can accurately distinguish most benign nodules and papillary cancers. However, cytological features do not distinguish benign from malignant follicular neoplasms, and cystic papillary thyroid cancers are a common cause of false negative results. Importantly, only 15% of cytological follicular neoplasm will ultimately be follicular carcinomas; therefore, 85% of individuals that undergo surgery for these nodules will have done so unnecessarily. Finally, by its nature, cytopathologic interpretation of FNA samples is subjective. For these reasons, the application of molecular analysis to better characterize thyroid nodule cytologic samples has been an area of intense interest.

With the advent of methods, such as reverse transcriptase-polymerase chain reaction (RT-PCR), in which tiny amounts of samples are suitable for analysis, and increases in the number of antibodies suitable for immunocytochemistry, the possibility of improving FNA-based characterization of thyroid nodules is now possible. In the initial section of this review, several of the most carefully studied molecular markers (Table 1) for thyroid FNA will be discussed.

Telomerase

Telomeres are chromosomal end structures, consisting of tandem repeats of TTAGGG that play a critical role in the protection of chromosomes during cell division and are important in chromosome positioning during replication (1). Chromosomes typically lose about 50 to 200 nucleotides of telomeric sequence from chromosomal ends per cell division because DNA polymerase is unable to replicate the ends of linear DNA. The resultant progressive shortening of chromosomes as cells divide has been described a cellular "biological clock"; once the chromosomes are shortened to a critical length through telomeric loss, cell growth stops and apoptosis is induced. Therefore, preservation of chromosomal end length during division would be expected to retard this natural "aging" of cells and result in continuous cell growth.