4. MOLECULAR EVENTS IN FOLLICULAR THYROID TUMORS

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INTRODUCTION

The analyses of human thyroid tumor tissues have proven informative in identifying key molecular events in epithelial neoplasia. The thyroid gland gives rise to a variety of epithelial tumors that differ markedly in their biologic patterns. The accessibility of thyroid tumors provides a tractable opportunity to define mechanisms of epithelial cell transformation in a spectrum of related cancers.

Two primary issues must be considered when investigating molecular genetic alterations within human thyroid tumor groups. The first is tumor classification. Thyroid tumors are classified predominantly on the basis of morphologic features interpreted by pathologists. Morphologic features provide initial biologic and clinical information but they have been defined somewhat non-specifically in retrospective series. Thus, thyroid tumor diagnosis can be imprecise [1–4] and can create confusion when correlating molecular genetic alterations with clinical and pathologic features. Mutations that predominate in one thyroid tumor group may be identified in others and the distinction as to whether such tumors are misclassified or contain additional alterations is difficult to ascertain. A second important issue relates to mutation detection. Polymerase chain reaction-based amplification and sequencing of nucleic acids from fresh or fast-frozen tissues are most often employed. Such assays are exquisitely sensitive and prone to cross-contamination, particularly when poorly preserved or archival tissues are used. Polymerase chain reaction can even detect genetic alterations within a minute sub-fraction of tumor cells. The biologic significance of this is often unclear. Tissue

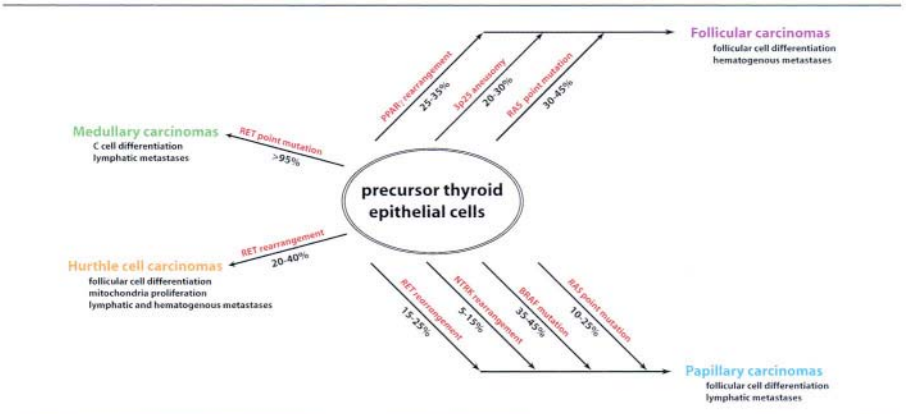

Figure 1. Histologic-Molecular Model of Thyroid Cancer Formation. Four main types of thyroid carcinoma with distinct biologic features are recognized. A subset of each type may progress to poorly differentiated and/or clinically aggressive forms. Genetic alterations that characterize these pathways and sub-pathways are shown.

composition must also be documented rigorously because thyroid tumor resections contain admixtures of tumor, normal thyroid, lymphoid, reactive and stromal elements. All such factors must be considered or erroneous results will be obtained [5–7].

This chapter begins with a histologic-molecular model of thyroid cancer formation and discusses known mutations and emerging biologic and clinical correlates in follicular thyroid tumors. A summary and comparison of thyroid carcinomas with the acute myeloid leukemias follows.

A histologic-molecular model of thyroid cancer

A model that encompasses histologic, molecular, and biologic facets of thyroid cancer formation is shown in Figure 1. At least four sub-types of thyroid cancer with distinct characteristics are recognized. Tumors within each group may progress to poorly differentiated, metastatic, and/or anaplastic forms. The thyroid carcinoma model seems unique relative to other carcinomas in several respects. First, distinct gene mutations define separate pathways of oncogenesis within the thyroid. This is different than a single linear genetic pathway envisioned commonly for other carcinomas such as those arising in the colon [8] and exocrine pancreas [9, 10]. Second, both thyroid specific and non-thyroid specific mutations characterize different thyroid carcinoma subgroups. One particularly interesting class of thyroid-specific mutations is the chromosomal rearrangements that encode gene fusions [11, 12]. Gene fusions been identified infrequently in carcinomas even though they are common in blood cell and soft connective tissue cancers [13]. Third, thyroid cancer mutations correlate with specific biologic properties. For example, *RET* and $PPAR\gamma$ rearrangements characterize papillary [14] and follicular [12] thyroid carcinomas that tend to spread via regional lymphatics or blood vessels, respectively. Distinct *RET* germ line point mutations identify different familial medullary thyroid carcinoma patients with propensities for poor