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An update on molecular biology of thyroid cancers

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Contents

Abstract

Differentiated thyroid cancer (DTC) is the most common endocrinological malignancy. There are several histological variants such as papillary and follicular thyroid carcinoma. Many patients with well-differentiated subtypes of DTC are cured by surgery alone or with

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radioiodine, while poorly differentiated types usually have a worse prognosis. The aggressiveness of thyroid tumors is closely linked to specific gene alterations.

Several diagnostic and prognostic molecular markers such as BRAF and RAS point mutations; RET/PTC and PAX8/PPARγ gene rearrangements; MAPK, PI3K, p53, Wnt–beta catenin, HIF1α and NF-kappaB signaling pathways; microRNA profiles and aberrant methylation have been demonstrated in more than 70% of DTC. Diagnostic use of these molecular markers may be optimized for identifying higher risks of mortality, tumor recurrence and metastatic potential. Understanding the molecular biology of thyroid cancers can be an important avenue for diagnosis and treatment of radioiodine-refractory or inoperable DTC patients with novel molecular targeted therapeutic agents.

Keywords: Thyroid cancer; Differentiated thyroid cancer; Molecular biology; BRAF; RET/PTC; PAX8/PPARγ

1. Introduction

Thyroid cancer is the most common malign endocrine neoplasm originating from follicular or parafollicular thyroid cells. Histopathological classification of thyroid tumors is critical for patient management and for determining the clinical course of the disease. Follicular thyroid cells derived from histological subtypes are follicular thyroid carcinoma (FTC), papillary thyroid carcinoma (PTC), poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma (ATC). FTC and PTC are classified as differentiated thyroid carcinoma (DTC). Poorly differentiated and ATC also originate from follicular cells, and many cases are believed to develop as a result of dedifferentiation of a well-differentiated papillary or follicular carcinoma. Medullary thyroid cancer (MTC) is derived from parafollicular or C cells which are included in the neuroendocrine tumor family; MTC may be a part of multiple endocrinological malignancy type II (MEN II) [1–3].

In the United States, approximately 23,500 new DTC cases are diagnosed each year and its incidence has continuously increased in the last three decades all over the world except for a few countries (such as Norway and Sweden). Recent reports indicated that there were 3- to 5-fold increases in incidence rates from 1980 to 1997 depending on age, gender, histological type of thyroid cancer, radiation exposure, geographical region and other factors. The highest increase in incidence was found in PTC [4]. Frequent use of sensitive diagnostic techniques such as high-resolution ultrasonography, computerized tomography, magnetic resonance or positron emission tomography may be responsible for incidental detection of thyroid tumors. Additionally, true increases in incidence rates of thyroid cancers can also be explained with increased environmental radiation and use of medical radiation, iodine intake, the Chernobyl disaster, carcinogens, environmental, ethnic and genetic factors or combinations of these factors [4–7].

The most frequent type of thyroid cancer is PTC constituting 75–85% of all cases. Multifocality, lymphatic or local spreading and lymph node metastases are characteristic features of PTC whereas distant metastases by hematogenous spreading are relatively uncommon. The overall 5 and 10-year survival rates of PTC are approximately 97% and 93%, respectively [6,8,9]. In most low risk patients with small tumors, no local or distant metastases and extrathyroidal infiltration, surgery and post-surgical radioiodine ablation therapy is usually adequate. Moreover, for PTC patients with <1 cm tumor size, surgical treatment alone may be sufficient. Metastatic doses and repeated radioiodine therapy have been used for patients with lymph node or distant metastases and extrathyroidal soft tissue spreading [10–13]. PTCs are the predominant histological type in children with thyroid cancer and in patients with head-and-neck irradiation history. The clinical course of these patients is relatively worse because of the aggressive behavior of these tumor [3,6,8]. PTCs frequently have genetic alterations such as point mutations of BRAF and RAS genes and RET/PTC rearrangements. These genetic alterations are found in more than 70% of the patients and may have prognostic implications [14–17].

FTC is second most common thyroid malignancy and accounts for 10–15% of thyroid cancers [6,8]. FTC tends to metastasize to lung and bone *via* the bloodstream. Prognosis of FTC is worse than PTC especially in patients with distant metastases. The overall 5 and 10-year survival rates for follicular thyroid cancer are 91% and 85%, respectively. Treatment strategy is thyroidectomy followed by ablative or metastatic doses of radioiodine therapy [12,13,18,19]. Approximately 50% of FTC patients have mutations in RAS family genes or PAX-PPARγ rearrangements [14,20,21].

ATC is an uncommon, lethal malignancy of older adults. The mean survival time is usually less than 6 months from the time of diagnosis and this outcome is not altered by current treatments. Patency of the airway is critical for the patient's course due to aggressive local spreading of the primary tumor and airway obstruction is the primary cause of death in most patients [1].

Thyroid follicular cells trap iodine by a Na^+/I^- Symporter (NIS), which is an energy-dependent transport system regulated by thyroid stimulating hormone (TSH). Iodine is organified by thyroid peroxidase (TPO) at the apical surface of the thyroid cells and then conjugated to thyroglobulin (Tg). Iodine is also trapped and organified by DTC cells as in thyrocytes and this unique characteristic plays the most important role on treatment and diagnosis of DTC [22–24]. 131 Iodine (^{131}I) is a β and γ emitting radionuclide and chemically identical to the non-radioactive form of iodine. Radioiodine is an effective therapeutic and imaging agent for DTCs. Dedifferentiated, poorly differentiated and anaplastic thyroid tumor cell clones have lost the ability to trap iodine. Thus, radioiodine is not effective for detection and therapy of these tumors