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Molecular Pathology of Thymic Epithelial Neoplasms

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Thymomas are epithelial tumors thought to derive from the thymic epithelial cells. Although thymomas are infrequent tumors, with an incidence of one to five cases out of every 1 million individuals per year, they represent the most common tumors of the anterior mediastinum [1]. In general, thymomas are indolent tumors with a tendency toward local recurrence rather than metastasis. However, thymic carcinomas–that is, thymic epithelial tumors that exhibit cytologic atypia–are typically invasive, with a high risk of relapse and death [1–3].

The etiology of thymic tumors is unknown and their molecular features are starting to be delineated [4–9]. A better understanding of the molecular characteristics of the different histologic and clinical types of thymomas could provide meaningful information to develop novel strategies to improve their diagnosis, therapy, and prognosis. This article describes the recent advances in the knowledge of the molecular basis of thymoma development, focusing on molecular changes that could explain differential tumor pathologic characteristics, outcome, and potential response to molecularly targeted therapy.

CLINICO-PATHOLOGIC FEATURES OF THYMIC TUMORS

Thymoma classification has been a challenging field in pathology because of the wide heterogeneity of these tumors from the viewpoint of pathology, clinical characteristics, and prognosis. The so-called "histogenic" classification, which tried to reflect the major functional and anatomic compartments of the thymus, distinguished medullary, mixed, predominantly cortical and cortical thymomas, and well-differentiated thymic carcinoma [10–13]. In 1999, the World Health Organization (WHO) histologic classification of thymic tumors proposed a very complex classification, which distinguishes six types of tumors (thymoma

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types A, AB, B1, B2, and B3; and thymic carcinoma, or type C) based on morphologic features combined with the limited functional and molecular information available [1]. During the same year, Suster and Moran [14] proposed a drastic simplification of the previous thymomas classifications (thymomas, atypical thymomas, and thymic carcinomas), based on the belief that primary epithelial tumors of the thymus are part of a continuum from well differentiated to poorly differentiated neoplasms. These investigators claim that tumor staging (ie, invasion of the capsule and tumor resectibility), not histopathologic typing, has a more crucial role for accurate and reliable prognostication for the better differentiated forms of these tumors (reviewed in Ref. [15]).

MOLECULAR PATHOGENESIS OF THYMIC TUMORS

Currently, there is widespread acceptance that the neoplastic transformation of normal epithelial cells represents a multistep accumulation of genetic and epigenetic alterations, including abnormalities for the activation of oncogenes and inactivation of tumor suppressor genes (TSG). While oncogenes and TSGs are required for normal cell proliferation and differentiation, their aberrant expression leads to abnormal cell proliferation and tumor development. Oncogenes have a role in signal transduction and in the regulation of gene expression, such as activating mutation or amplification leading to cells' growth stimulation. TSGs are negative regulators of cell proliferation and are inactivated by genetic (mutation, deletion, rearrangement, and duplication) and epigenetic (methylation of gene promoters) changes. In addition to those specific genetic changes, other evidence indicates that genetic instability occurs in tumor development. This evidence includes changes in the size of short-tandem DNA repeats or microsatellite repeats, also known as microsatellite instability [16].

While considerable progress has been made in understanding the molecular pathogenesis of most human neoplasms, current knowledge about the genetic changes involved in the development of thymic tumors is very limited. However, their molecular abnormalities can be systematically reviewed using Hanahan and Weinberg's [17] "hallmarks of cancer." These changes include (1) self-sufficiency in growth signaling; (2) insensitivity to antigrowth signals; (3) ability to evade apoptosis; (4) limitless replicative potential; (5) ability to sustain angiogenesis; and (6) tissue invasion and metastasis.

Self-Sufficiency in Growth Signaling: Oncogenes

Many growth factors and their receptors are abnormally expressed by cancer cells and adjacent stromal cells, producing autocrine and paracrine growth stimulation loops. Several of those factors and receptors are encoded by proto-oncogenes that become activated by various mechanisms during the development of human cancers [17]. Several growth factors or regulatory peptides and their receptors have shown to be overexpressed by thymic tumor cells, and thus may provide a series of autocrine and paracrine growth stimulatory loops in this neoplasm. Oncogenes that contribute to the pathogenesis of