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editorial

Emerging molecular prognostic markers in human thyroid carcinoma

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The neoplasms derived from the follicular thyroid cell represent the most common endocrine malignancy, accounting for ≃ 2% of all new malignant diseases and ≃ 0.4% of deaths related to cancer. Its estimated incidence in USA ranks, along with the melanoma of the skin and the non-Hodgkin lymphoma, as the fifth most common cancer in women (1, 2). The large majority of thyroid cancers are represented by the differentiated (DTC) papillary (PTC) and follicular (FTC) thyroid carcinomas which, following dedifferentiation, are thought to give rise to the lethal anaplastic thyroid carcinomas (1-5). Although derived from the same cell type, the different thyroid neoplasms show specific histological features, biological behavior and degree of differentiation as a consequence of different oncogenic events (1). The constitutive activation of the mitogen-activated protein kinases (MAPK) pathway is held responsible for the cancerogenesis of PTC (1). Three genetic alterations, mutually exclusive, have been associated with the abnormal activation of the MAPK pathway in the vast majority of PTC: the RET/PTC (REarranged during Transfection/Papillary Thyroid Cancer) rearrangements, activating mutations of the three RAS (RAt Sarcoma viral oncogene homolog) proto-oncogenes (H-RAS, K-RAS and N-RAS) and of the BRAF (v-Raf murine sarcoma viral oncogene homolog B1) gene. Also in the FTC the activation of the MAPK pathway plays a role in tumorigenesis. Differently from the PTC, however, neither RET/PTC rearrangements nor BRAF mutations have been found in FTC, while the presence of RAS mutations is frequently observed. The FTC are also characterized by different genetic alterations which are not involved in the activation of the MAPK pathway and elicit different molecular effects, including the paired box gene 8/peroxisome proliferator-activated receptor (PAX8/PPAR rearrangements (1). Additional molecular events involved in the progression of DTC to poorly differentiated and anaplastic thyroid cancer include inactivating mutations of the p53 tumor suppressor gene and activating mutations of the CTNNB1 gene encoding the β-catenin (1).

The prognosis for the DTC is generally favorable with a 10 years survival rate of about 90% (6). It has to be mentioned, however, that over the last two decades our ability to identify DTC patients at risk of recurrences or of disease-related death, mostly based on clinicopathological factors such as tumor size, extent of the cancer and patient's age, has not improved. As a consequence, still today about 20% of patients face the morbidity of disease recurrences and DTC-related deaths (7). Thus the identification of molecular marker(s) to refine the stratification risk of DTC patients is of particular interest. Aim of the present editorial is to describe some new emerging molecular prognostic markers which may become of practical interest to surgeon.

Following the advances made in the comprehension of the molecular mechanisms involved in thyroid cancer progression, several studies have been performed in order to associate the common genetic alterations, above mentioned, with the aggressiveness of DTC. Among these only the BRAF V600E mutation, observed in 29-87% of PTC cases, has been suggested to represent a new molecular prognostic marker for the PTC (8). Actually, different studies suggest an association between

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the presence of BRAF mutations and poor prognostic factors including older age, extrathyroidal invasion, multicentricity, presence of lymph node or distant metastasis, advanced stage of disease and higher likelihood of recurrent or persistent disease (8). However, despite the initial enthusiasm a debate is ongoing about its clinical use as a prognostic marker (8). Indeed, several investigators did not confirm the association between the presence of the BRAF V600E mutation and the clinical outcome (8). More importantly, the frequency of BRAF mutations in PTC is high, being on average present in 45% of PTC patients, and in some case studies reported in more than 80% of PTC cases. This is in contrast with the low percentage of PTC patients (about 20%) who face the morbidity of disease recurrences and DTC-related deaths (8). Therefore, if the BRAF mutations would be used in clinical practice as a poor prognostic factor a considerable proportion of patients, now considered at low risk, would be shifted in a high risk group and exposed to overtreatment. Thus, further studies are needed to clarify this complex issue.

Recent experimental evidence have suggested a prognostic role of the components of the urokinase plasminogen activating system (uPAS) in PTC. The uPAS consists of the serine protease urokinase (uPA), its cognate cell membrane receptor (uPAR) and two main inhibitors belonging to the serine proteinase inhibitors (serpin) superfamily, the plasminogen activator inhibitor 1 (PAI-1), and 2 (PAI-2) (9). It is implicated in numerous pathophysiological processes requiring the remodelling of extracellular matrix and basement membranes, such as wound healing, tissue regeneration and involution, immune response, angiogenesis and tumor progression. In the latter, beside having a pivotal role in extracellular matrix degradation allowing tumor enlargement and scattering, it also affects multiple aspects of the neoplastic evolution, such as tumor cell proliferation, adhesion and migration, intravasation and extravasation, growth at the metastatic sites and tumor neoangiogenesis (9). In agreement with their role in cancer progression and metastasis, an increased expression of uPA, uPAR, and PAI-1 has been documented in several malignant tumors including thyroid cancer, as below described. Importantly, a correlation between the expression levels of one or more uPAS members and a poor prognosis has been reported for different cancer types including gastric, colorectal, endometrial and prostate cancer (9). The prognostic value of uPAS in human malignancies is particularly evident in breast cancer, for which it has been demonstrated that patients with high levels of uPA activity in cancer tissues had a significantly shorter disease-free interval. Moreover, uPA was as prognostic factor stronger than tumor size, nodal and estrogens receptor status, being in node-negative patients the best predictor of DFI and overall survival (10, 11). The prognostic relevance of uPA and PAI-1 in breast cancer has been validated by Level 1 Evidence studies comprising a prospective randomized multicenter trial and a retrospective pooled analysis (10, 11). Although uPA and PAI-1 have a prognostic value in the general population of breast cancer patients, their main clinical use is in node-negative patients, for which the assessment of low tissue levels of both proteins can avoid over-treatment with adjuvant chemotherapy (10, 11). The proved ability of uPA and PAI-1 to guide therapeutic decision making has lead the American Society of Clinical Oncology to include them among the recommended breast tumor markers for use in practice (12).

In thyroid cancer, the first evidence of uPA implication in human thyroid tumor invasivity was provided by Packman *et al*. (13), who found an increase of uPA activities in a follicular thyroid carcinoma cell line derived from lung metastasis, with respect to the less invasive clone derived from lymph node metastasis. Subsequent studies described the diffuse expression of uPA, uPAR, and PAI-1 in the majority of thyroid carcinomas and the association of high uPAR expression with poorly-differentiated and more aggressive PTC (9). More recently, it has been shown the augmented expression of uPA, uPAR, and PAI-1 in PTC tissues with respect to normal matched thyroid tissues, and a significant association between increased uPA expression and the main thyroid cancer prognostic factors such as tumor size and lymph node metastases (14). In a different study the levels of uPA and PAI-1 proteins have been shown to be markedly different among various histological types of thyroid cancer, exhibiting the lowest values in adenomas and the highest in anaplastic carcinomas (15). Furthermore, uPA and PAI-1 proteins were found higher in tumors with extrathyroidal invasion or distant metastasis and in those exceeding 1 cm of diameter. More interestingly, in this study the survival analysis revealed a significant impact of both uPA and PAI-1 on the survival rate, providing new indications of the potential prognostic relevance of uPAS components in thyroid tumors (15). Later, also the increased level of uPAR protein has been associated with advanced pT- or M-stages and poor survival (16). In the recent years, our group has been involved in a research project aimed to define the role of the uPAS in thyroid cancer progression as well as in

its evaluation as potential prognostic factor (9, 16, 17). In particular, we recently demonstrated that high expression of the uPA and its cognate receptor (uPAR) was associated with advanced stages and reduced disease-free interval in papillary thyroid carcinomas, and that this association was particularly evident in stage I patients, actually considered at low risk of recurrences (17).

In conclusion, there is an overall agreement in the literature documenting the augmented expression of uPA, uPAR, and PAI-1 in thyroid cancers. Importantly, different studies demonstrated a clear correlation between increased expression of uPAS components and some of the major prognostic factors for thyroid cancer such as tumor size, lymph node or distant metastases, as well as with patients survival and disease-free interval. If validated on larger case study, these findings may help to better define the prognosis, make informed therapeutic decisions and develop tailored prevention programs especially for stage I PTC patients, actually considered at low risk to develop disease recurrences.

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