CD147 expression as a significant prognostic factor in differentiated thyroid carcinoma

HUI TAN, KE YE, ZHIMING WANG, and HUIHUAN TANG

HUNAN, CHINA

CD147 is 1 of the molecules involved in regulating the expression of matrix metalloproteinases (MMPs). The goal of this study was to analyze the expression of CD147 in differentiated thyroid carcinoma (DTC) tissues as well as its association with the clinicopathologic features of DTC patients and its prognostic significance. During our research, CD147 expression in 156 patients who underwent operation for DTC (100 with papillary thyroid carcinoma (PTC) and 56 with follicular thyroid carcinoma (FTC)) were examined by immunostaining on paraffin-embedded tumor specimens. Then, the association of CD147 expression with clinicopathologic characteristics and patients' prognosis was analyzed. As a result, CD147 was expressed in cancerous lesions but not in normal tissues. Overall, 55 of 156 (35.26%) cases showed low CD147-positive expression, 52 of 156 (33.33%) showed intermediate CD147-positive expression, and 49 of 156 (31.41%) showed high CD147-positive expression. Positive CD147 staining was associated significantly with various clinicopathologic features, such as extrathyroidal invasion ($P = 0.02$), lymph node metastasis ($P = 0.01$), and depth of tumor invasion ($P < 0.01$). Patients with low CD147 expression showed better survival rates than those with intermediate and high expression (90.91% for low expression, 82.69% for intermediate expression, and 65.31% in high expression, respectively; $P < 0.05$ for analyses). Using Cox regression analysis of the 156 patients, high expression of CD147, extrathyroidal invasion, lymph node metastasis, and the pathologic grading of tumor invasion seemed to be independent prognostic indicators ($P < 0.01$, $P = 0.02$, $P < 0.01$, and $P < 0.01$, respectively). Therefore, we conclude that the expression of CD147 may be useful to predict the prognosis of DTC patients. (Translational Research 2008;152:143–149)

Abbreviations: DTC = differentiated thyroid carcinoma; ECM = extracellular matrix; EMMPRIN = extracellular matrix metalloproteinase inducer; FTC = follicular thyroid carcinoma; MMP = matrix metalloproteinase; PTC = papillary thyroid carcinoma

Thyroid carcinomas are rare malignancies and are roughly divided into differentiated thyroid carcinoma (DTC), undifferentiated thyroid carcinoma according to histologic criteria.[1] Surgical resection is the main modality of treatment for DTC, including papillary thyroid carcinomas (PTCs) or follicular thyroid carcinomas (FTCs), with generally favorable results. The disease-specific overall survival rate at 10 years is approximately 80% to 90%.[2] However, some patients develop metastases and recurrent disease, and this disease course is often correlated with a worse clinical outcome. Several clinicopathologic factors have been reported to be significant in the prognosis of DTC, such as age at diagnosis, local tumor size, extracapsular invasion, and distant metastasis.[3–6] However, the markers that could predict patients with a lower risk of suffering a poor outcome from those with a higher risk of suffering a poor outcome are lacking. Therefore,

From the Department of General Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China.

Submitted for publication March 24, 2008; revision submitted June 4, 2008; accepted for publication July 16, 2008.

Reprint requests: Huihuan Tang, Department of General Surgery, Central South University, Xianya Hospital, Changsha, Hunan, China; e-mail: tanhui@medmail.com.cn.

1931-5244/$ – see front matter

doi:10.1016/j.trsl.2008.07.005

AT A GLANCE COMMENTARY

Background

Surgical resection is the main modality of treatment for differentiated thyroid carcinoma (DTC) with generally favorable results. However, a few DTC patients develop metastases and recurrent disease, and this disease course is often correlated with a worse clinical outcome. A paucity of markers could predict patients with a lower risk of suffering a poor outcome from those with a higher risk of suffering a poor outcome. To our knowledge, CD147 is 1 of the molecules involved in regulating the expression of MMPs. Therefore, the goal of this study was to analyze the expression of CD147 in DTC tissues as well as its association with the clinicopathologic features of DTC patients and its prognostic significance.

Translational Significance

As a result, we found that CD147 was expressed in cancerous lesions but not in normal tissues. Moreover, high expressions of CD147, extrathyroidal invasion, lymph node metastasis, and the pathologic grading of tumor invasion have been demonstrated to be independent prognostic indicators for DTC.

it is important to find biologic factors that affect disease recurrence and the survival of patients with DTC.

The extracellular matrix (ECM) metalloproteinase inducer [CD147/extracellular matrix metalloproteinase inducer (EMMPRIN)] is a member of the immunoglobulin superfamily of adhesion molecules, and it can activate several matrix metalloproteinases (MMPs), which are members of zinc-dependent proteolytic enzymes and play a central role in the processes of local invasion and distant metastasis of tumors because of their ability to break down basement membranes and most ECM components.[7–9] Many metastasis-associated and regulatory elements have been known to influence and be influenced by MMP. So, CD147 expression may be very important for the progression of tumors. More observations on CD147 expression between tumor entities have been documented, such as squamous-cell carcinomas, pancreatic carcinoma, renal carcinoma, hepatoma, medullary breast adenocarcinomas, and glioblastoma, which are all associated with a particularly high incidence of CD147 expression.[10–12] However, a paucity of research seems to be concerned with CD147 expression in thyroid carcinomas. For this reason, the goal of the current study was to investigate the immunohistochemical expression of CD147 in DTC tissues and its prognositic utility.

MATERIALS AND METHODS

Patients and tissue samples. Surgical specimens were obtained from 156 patients with DTC (100 with PTC and 56 with FTC) who had undergone a resection of primary thyroid carcinoma at the Department of Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China, from January 1992 to January 1997. The subjects included 28 men and 128 women ages 16 to 88 years (46.16 $\pm$ 18.92 years). The resected thyroid tissues had been macroscopically examined to determine the location and size of the tumors. Samples obtained from the thyroid lesions and dissected lymph nodes were fixed in 10% formalin and were routinely processed for paraffin embedding. Histologic sections cut at 4 μm were stained with hematoxylin and eosin, as well as with immunoperoxidase procedures (avidin−biotin complex method). Histologic sections were reclassified independently by 2 experienced pathologists according to histologic typing of the World Health Organization as PTC or FTC to examine the extent and mode of invasion in the thyroid, lymph node metastasis, and histologic subtype.

After surgery, all patients were given a follow-up with time that ranged from 1 to 10 years (follow-up was performed by the time of December 2007). In addition, normal thyroid tissues were offered by the Pathology Department of Xiangya Hospital. All patients who died of other diseases rather than of DTC and unexpected events were excluded from the case collection. The study was approved by the Research Ethics Committee of Xiangya Hospital. Informed consent was obtained from all patients. All specimens were handled and made anonymous according to the ethical and legal standards.

Immunohistochemical staining and assessment. For immunohistochemical staining, tissues were fixed in 10% buffered formalin and embedded in paraffin. Commercially available monoclonal antibodies to CD147 (Santa Cruz Biotechnology, Santa Cruz, Calif) were used. Immunohistochemical staining was carried out on TMA sections using the avidin−biotin method and a commercially available kit (Vectastain Elite ABC kit; Vector Laboratories, Burlingame, Calif). One paraffin-embedded block of thyroid tissue was selected from each case and cut into 4-μm sections. Deparaffinized sections were treated with methanol that contained 3% hydrogen peroxide for 10 min before conducting antigen retrieval using a microwave oven at 95°C for 5 min and cooling at 25°C for 2 h. After washing with PBS, blocking serum was applied for 10 min. The sections were incubated with an anti-CD147 monoclonal antibody overnight at 4°C. After washing in PBS, a biotin-marked secondary antibody was applied for 10 min followed by a peroxidase-marked streptavidin for an additional 10 min. The reaction was visualized by using 3, 3′-diaminobenzidine tetrahydrochloride. The nuclei were counterstained with hematoxylin. Positive and negative immunohistochemistry controls were routinely used. Reproducibility of staining was confirmed by reimmunostaining via the same method in multiple, randomly selected specimens.