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ORIGINAL ARTICLE

Cadherin-6 promotes EMT and cancer metastasis by restraining autophagy

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The transdifferentiation of epithelial cells toward a mesenchymal condition (EMT) is a complex process that allows tumor cells to migrate to ectopic sites. Cadherins are not just structural proteins, but they act as sensors of the surrounding microenvironment and as signaling centers for cellular pathways. However, the molecular mechanisms underlying these signaling functions remain poorly characterized. Cadherin-6 (CDH6) is a type 2 cadherin, which drives EMT during embryonic development and it is aberrantly re-activated in cancer. We recently showed that CDH6 is a TGFβ target and an EMT marker in thyroid cancer, suggesting a role for this protein in the progression of this type of tumor. Papillary thyroid carcinomas (PTCs) are usually indolent lesions. However, metastatic spreading occurs in about 5% of the cases. The identification of molecular markers that could early predict the metastatic potential of these lesions would be strategic to design more tailored approaches and reduce patients overtreatment. In this work, we assessed the role of CDH6 in the metastatic progression of thyroid cancer. We showed that loss of CDH6 expression profoundly changes cellular architecture, alters the inter-cellular interaction modalities and attenuates EMT features in thyroid cancer cells. Using a yeast two-hybrid screening approach, based on a thyroid cancer patients library, we showed that CDH6 directly interacts with GABARAP, BNIP3 and BNIP3L, and that through these interactions CDH6 restrains autophagy and promotes re-organization of mitochondrial network through a DRP1-mediated mechanism. Analysis of the LIR domains suggests that the interaction with the autophagic machinery may be a common feature of many cadherin family members. Finally, the analysis of CDH6 expression in a unique cohort of human PTCs showed that CDH6 expression marks specifically EMT cells. and it is strongly associated with metastatic behavior and worse outcome of PTCs.

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INTRODUCTION

Thyroid tumors are the most common malignancies of the endocrine system.[1] Papillary thyroid carcinomas (PTCs) account for almost 90% of the thyrocyte-derived cancers. PTCs are usually indolent lesions characterized by a slow rate of growth and a low-metastatic potential. Distant metastases arise in < 5% of patients and survival rate is over 90% (over 98% in young patients) in the first 10 years after diagnosis.[2,3] In spite of the low-risk profile, all patients who are diagnosed with PTCs are treated with invasive and aggressive approaches.[4,5] Thus, a major clinical challenge is currently to distinguish in the early stage of diagnosis patients who need aggressive treatments to reduce mortality from those who do not. Identification of markers that are specifically associated with the aggressive behavior of thyroid tumor cells should help overcome this hurdle.

The epithelial-to-mesenchymal transition (EMT) is a multistep process through which the epithelial cells shed their differentiated characteristics to undergo changes in morphology, architecture, adhesion and motility.[6–8] The ultimate result of this process is to confer migration properties to tumor cells. Adhesion molecules like cadherins have a crucial role in EMT. Cadherins are a family of transmembrane proteins, the major functions of which are to dictate the modalities of cell interaction with the microenvironment, and to mediate the organization of cytoskeleton and the structural architecture of the cells.[9] Biophysical forces applied by cell–cell or cell–ECM adhesion are translated into the cells by cadherins, and mediate the organization of cytoskeleton and the architecture of the cells. Beside this structural function, cadherins have a more complex role, acting as chemical and biophysical sensors of the surrounding microenvironment and as signaling centers for pathways controlling cell growth, fate and behavior.[10–14] The molecular mechanisms underlying the signaling function of cadherins are still poorly characterized.

Cadherin-6 (CDH6) is a class II cadherin involved in the morphogenesis of central nervous system and kidney.[15–18] As many proteins involved in embryogenesis, CDH6 is aberrantly re-activated in cancer.[19,20] Recently, we found CDH6 as strongly expressed in a model of highly aggressive thyroid cancer, and we showed that CDH6 expression is induced by TGFβ during EMT in thyroid cancer cells.[21,22] These observations suggest that CDH6 is part of a program that supports aggressiveness of thyroid tumors. In this work, we investigated the biological role of CDH6 in thyroid

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