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REVIEW ARTICLE

Molecular biomarkers involved in the tumor dedifferentiation process of thyroid carcinoma of epithelial origin: perspectives☆

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Abstract Although papillary or follicular well-differentiated thyroid carcinoma usually has a good prognosis, a proportion of well-differentiated thyroid carcinomas show a more aggressive behavior with local recurrence and metastases, either at diagnosis (in less than 5% of cases) or over time. Although there are several scoring systems to assess prognosis of well-differentiated thyroid carcinoma, mainly based on clinical and pathological data, there is currently no valid criterion to define an adequate, differential treatment for patients with low risk carcinomas as compared to those with more aggressive tumors. Identification of patients with a high risk at the time of diagnosis would be essential to develop new therapeutic strategies and to improve follow-up, and molecular biomarkers could be a highly useful tool for this purpose.

PALABRAS CLAVE
Carcinoma de tiroides;
Desdiferenciación;
Marcadores moleculares

Biomarcadores moleculares implicados en el proceso de desdiferenciación tumoral del carcinoma de tiroides de origen epitelial: perspectivas

Resumen Aunque el carcinoma diferenciado de tiroides, papilar o folicular, tiene habitualmente un buen pronóstico, existe un porcentaje de casos que presentan un comportamiento más agresivo con recurrencias locales y metastatización, ya sea en el momento del diagnóstico (en menos de un 5% de los casos) ya en el seguimiento. A pesar de que existen diferentes sistemas de evaluación del pronóstico del carcinoma diferenciado de tiroides, basados especialmente en datos clínicos y patológicos, no hay en la actualidad un criterio válido que permita definir un tratamiento diferencial entre los pacientes con carcinomas de bajo riesgo y aquellos con carcinomas más agresivos. La identificación de los pacientes de riesgo en el momento del

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diagnóstico sería clave para desarrollar nuevas estrategias terapéuticas y mejorar el seguimiento, siendo en este sentido los biomarcadores moleculares una herramienta de gran valor.

Introduction

Differentiated thyroid carcinoma is the most common endocrine neoplasm, with an increasing incidence in recent years.[1,2] More than 90% of these tumors have their origin in follicular cells, and they are classified as well differentiated carcinoma (DTC), including the papillary (PTC) and follicular (FTC) variants, and undifferentiated or anaplastic carcinoma (ATC). The latter is one of the most aggressive tumors, with a mean 5-month survival rate from the time of diagnosis and a one-year survival rate of only 20%.[3]

Most well differentiated tumors have a favorable clinical course, with survival rates close to 90% 10 years after diagnosis.[4–6] There is however a proportion of tumors with more aggressive behavior including local recurrence and metastases either at diagnosis (in less than 5% of cases) or follow-up, and it has been estimated that approximately 10–15% of patients with differentiated carcinoma will develop local or distant metastases.[7,8] Survival rates ranging from 49% to 68% have been reported 10 years after the occurrence of cervical metastases, which are responsible for one third of deaths related to the disease. Distant metastases occur in lung (50%), bone (25%), lung and bone (20%), and other sites (5%). The survival rate following the diagnosis of distant metastases decreases to 25–42%.[9]

The treatment of low-risk differentiated thyroid carcinoma has not changed substantially over the past decades and is based on surgery, ablation with ^{131}I, and suppressant treatment with levothyroxine,[10] although there is an increasing trend to base both treatment and follow-up recommendations on individualized risk assessment.[7,11] Most evaluation systems are based on clinical and pathological data, and different risk factors have been identified, including age at diagnosis, sex, size, the presence of metastasis, and the initial treatment used.[6,12,13]

The response rate to the standard treatment is high, with overall survival rates higher than 75%. However, patients with dedifferentiation processes (poorly differentiated thyroid carcinoma [PDTC]) who have iodine refractory disease (the presence of at least one lesion with no ^{131}I uptake or progression within one year of ^{131}I ablation) show a mean survival of 3–6 years after the diagnosis of distant metastases, and although growth is slow, most metastases progress. These patients are therefore candidates for other treatment modalities,[14] and one of the main objectives of clinicians is to distinguish this subgroup from DTCs of good prognosis.

It is therefore essential to know the process of dedifferentiation or anaplastic transformation of these tumors. Our understanding of the molecular biomarkers related to this process, and thus with prognosis and survival, has increased in recent years, so allowing for new therapeutic targets to be established.

Biomarkers: Definition

Biomarkers are defined as biological parameters that may be measured or detected and may in turn be correlated to a pathological process. However, for these parameters to be considered as true biomarkers, they must meet the following criteria, described by Herberman in 1977: (1) their measurement should be simple, reproducible, and easily available; (2) they should discriminate between normal and pathological states; (3) they should be highly sensitive and specific; and (4) they should be able to monitor recurrent disease processes.[15]

In recent years, the development of new technologies applied to the molecular understanding of disease has significantly contributed to the identification of new biomarkers, called molecular biomarkers. These new biomarkers have undoubtedly become highly relevant because they have made possible a deeper understanding of the etiopathogenesis of many diseases by identifying, at least partly, the molecular mechanisms involved, especially in neoplastic conditions, and have provided valuable diagnostic, prognostic, and therapeutic information. However, there are many factors, not only genetic or epigenetic, but also environmental, directly or indirectly involved in the development and metastatic progression of tumors, which often makes selection of these new biomarkers difficult. This is one of the most significant limitations in clinical practice. The different types of biomarkers in thyroid tumor disease are discussed below.

Serological markers

In epithelial thyroid tumors, thyroglobulin (TG), a glycoprotein produced by thyroid follicular cells, was one of the first tissue-specific biomarkers used. However, although this is a helpful serum marker for assessing the presence of residual or metastatic tumor in patients undergoing total thyroidectomy, many studies have reported that it is of no use in detecting populations at high risk of developing this type of tumor.[16] In addition, TG tests may not be reliable in patients on suppressing levothyroxine therapies and in patients who develop some types of benign conditions such as thyroiditis, thyrotoxicosis, thyroid adenoma, or iodine deficiency. In these latter cases, false positive results are frequently seen because of increased serum TG levels.[17]

Genomic and transcriptomic markers

It is well known that the process of carcinogenesis results from the random accumulation of genetic and epigenetic aberrations in tissue. At least 10–20% of gene expression