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Review article

Molecular biology of papillary thyroid microcarcinomas: What is new?

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ABSTRACT

Objectives: Papillary thyroid microcarcinoma (PTMC), a tumor that measures 1 cm or less, according to World Health Organization (WHO) histological classification of tumors, is the most common form of papillary thyroid carcinoma (PTC) comprising much more than half of all PTCs if one includes the so-called incidentalomas. Although PTMC has an excellent prognosis, a minority of cases were found to be clinically aggressive. We decided to perform a review of the literature on records on PTMC in attempt to find which molecular markers might be used as predictors of the clinical behavior of PTMC. This review article aims to summarize the molecular mechanisms that were associated to PTMCs described in the last 10 years, with a particular focus on the clinical importance of genetic alterations (BRAF mutation, RET/PTC rearrangement, NAD(P)H and NRH polymorphisms and TERT mutation) and anomalous expression of several molecules (P53, P27, COX-2, EGFR, ki-67, S100A4, cyclin D1, galectin-3, HMWK, CK-19, HBME-1, HGF, c-MET, membrane mucins and cell adhesion molecules).
Methods: We made a systematic search in the PubMed database using the keywords *papillary thyroid microcarcinoma* and reviewed all the articles published in the last 10 years, in English, addressing issues related to PTMC.
Results: Unfortunately, all genetic alterations and biomarkers reported to date have little potential per se to differentiate between indolent and aggressive PTMCs. Further studies using the aforementioned markers and, most likely, others are needed in order to try to find a combination of several markers that may be used for increasing the probability of identifying PTMC cases with more aggressive behavior, thus allowing the establishment of a more appropriately targeted treatment.

Biologia molecular dos microcarcinomas papilares da tiroide: o que há de novo?

Palavras-chave:
Cancro da tiroide
Microcarcinoma papilar da tiroide
Alterações genéticas

RESUMO

Objetivos: O microcarcinoma papilar da tiroide, um tumor que mede 1 cm ou menos, de acordo com a classificação histológica dos tumores da Organização Mundial da Saúde, é o tipo mais comum de carcinoma papilar da tiroide e, se incluirmos os chamados incidentalomas, corresponde a muito mais de metade de todos os carcinomas papilares da tiroide. Embora o microcarcinoma papilar da tiroide tenha um excelente prognóstico, uma minoria dos casos são clinicamente agressivos. Decidimos realizar uma revisão da literatura, na tentativa de encontrar marcadores moleculares que possam ser utilizados como preditores do comportamento clínico dos microcarcinomas papilares da tiroide. Este artigo de revisão pretende resumir os mecanismos moleculares que foram associados ao microcarcinoma papilar da tiroide, descritos nos últimos 10 anos, com um particular ênfase na importância clínica das alterações genéticas (mutação BRAF, rearranjo RET/PTC, polimorfismos NAD[P]H e NRH, e mutação TERT) e da expressão anormal de várias moléculas (P53, P27, COX-2, EGFR, ki-67, S100A4, cyclin D1, Galectin-3, HMWK, CK-19, HBME-1, HGF, c-MET, mucinas de membrana e moléculas de adesão celular).

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Métodos: Foi feita uma pesquisa sistemática na base de dados PubMed usando as palavras-chave *papillary thyroid microcarcinoma*, com subsequente revisão de todos os artigos relacionados com os microcarcinomas papilares da tiroide publicados nos últimos 10 anos, em inglês.
Resultados: Infelizmente, todas as alterações genéticas e biomarcadores reportados até à data têm, *per se*, pouco potencial para distinguir entre microcarcinomas papilares da tiroide indolentes e agressivos. Estudos adicionais utilizando os marcadores acima mencionados e, muito provavelmente, outros são necessários, no sentido de tentar encontrar uma combinação de vários marcadores que possam ser utilizados para aumentar a probabilidade de identificar os casos de microcarcinoma papilar da tiroide com um comportamento mais agressivo, permitindo assim estabelecer um tratamento mais apropriado e direcionado.

Introduction

Papillary thyroid microcarcinoma (PTMC) is defined, by the World Health Organization (WHO), as a small papillary thyroid carcinoma (PTC) measuring 10 mm or less in its greatest dimension.[1]

Thyroid cancer is the most frequent endocrine malignancy, representing 2% of all malignant diseases and is responsible for almost 90% of neuroendocrine cancers.[2,3] Eighty to 90% of thyroid cancers are PTCs and almost half of those are clinically evident PTMCs.[3,4]

The increasing incidence of small thyroid cancers was suggested to be caused by the use of sensitive screening imaging tools capable of identify subclinical disease in a way that, in countries with access to technology, 90% of incidental cases are due to low risk thyroid cancer. Besides that, there is no evidence of any clinical impact on mortality, so this increased incidence is probably an effect of overdiagnosis, reflecting our capacity to detect occult and indolent cancer.[5–7]

PTMCs usually have a benign behavior and do not affect patient survival.[8] Considering their excellent prognosis and low mortality rate, one would expect that PTMCs were an indolent disease.[9] However, in some cases, PTMCs have an aggressive behavior leading to loco-regional recurrence, distant metastasis and mortality.[10]

The predictive factors for this aggressively behavior have not been completely recognized, but clinicopathological factors such as age greater than 45 years, male gender, tumor size bigger than 5 mm, multifocality, lymph nodes metastasis (LNM) and extrathyroidal extension (ETE) have been reported as predictors of poor prognosis.[4,11] On the other side, many studies are trying to find the relationship between some molecular characteristics of PTMCs and their behavior. BRAF mutation, RET/PTC rearrangement, NAD(P)H and NRH polymorphisms, TERT mutation, and many molecular markers may play a role in PTMC behavior.

The uncertainty of the risk associated to PTMCs is probably responsible for the controversial management of these small tumors. It is not always easy to define the best way to manage these patients in terms of treatment and follow-up.

To estimate the prognosis and to find a marker or a combination of markers able to stratify the clinical risk in PTMC became an important issue due to the need of tools that may assist in defining the best therapeutic approach for patients with this kind of cancer.

In this review, we analyzed the molecular biology behind PTMC to contribute for the understanding of the influence of genetic alterations, molecular pathways and other biomarkers in PTMC behavior, having as an ultimate goal the identification of prognostic markers in this setting.

Methods

The literature was retrieved using PubMed and aided by manual searching. The terms *papillary thyroid microcarcinoma* were used as keywords connected by the Boolean operator AND. Inclusion criteria were: published in English literature and during the last 10 years.

The query obtained through the database was: papillary [All Fields] AND ("thyroid gland"[MeSH Terms] OR ("thyroid"[All Fields] AND "gland"[All Fields]) OR "thyroid gland"[All Fields] OR "thyroid"[All Fields] OR "thyroid (usp)"[MeSH Terms] OR ("thyroid"[All Fields] AND "(usp)"[All Fields]) OR "thyroid (usp)"[All Fields]) AND microcarcinoma[All Fields] AND english[Language] AND ("2004/11/30"[CRDAT]: "2014/11/30"[CRDAT]) AND ("2004/11/31"[PDAT]: "2014/11/31"[PDAT]) AND English[lang].

This research provided 410 potentially relevant articles. The articles that did not seem focused on molecular biology of PTMCs were excluded through title and/or abstract review. After that, 46 potentially relevant articles remained, which were evaluated in detail. Forty-five of them were selected, and the remaining one excluded.

Finally, automatic alert up to February 2015 provided one more article eligible for this review and 13 more articles were also manually included through bibliographic references from review articles, resulting in total of 59 articles.

Review

BRAFV600E mutation

B-type Raf kinase (BRAF), a serine/threonine-selective protein kinase, is involved in the mitogen-activated protein kinase (MAPK) pathway.[12] This signaling pathway is involved in the regulation of cell growth, division, and proliferation.[13] When constitutively activated, causes abnormal cell proliferation, adhesion, migration and invasion, leading to carcinogenesis.[8,12]

BRAFV600E, the consequence of a unique thymine-to-adenine transversion, represents more than 90% of all the mutations found in the BRAF gene and is a very specific sign for PTC.[12,14] Besides enhancing the capacity of BRAF mutated cells to proliferate and transform and the association with an increase in matrix metalloproteinases and desmoplastic stromal reaction, there are many roles attributed to BRAFV600E, namely: up-regulation of tumor promoting genes, down-regulation of tumor suppressor genes, angiogenesis, promotion of tumor growth, tissue invasion and extracellular matrix remodeling.[15–18]

The BRAFV600E mutation is the most common genetic alteration in PTC and has been associated with poor prognostic factors.[19] However, literature remains controversial in this question. With regard to PTMC, the utility of BRAFV600E mutation, detected in 15.8–52% of PTMC cases, as a prognostic factor is unclear.[13,14] Therefore, many efforts have been made to understand the role of this mutation.