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Review

Molecular features of thyroid oncocytic tumors

Giuseppe Gasparre[a,b], Elena Bonora[a], Giovanni Tallini[c], Giovanni Romeo[a,*]

[a] Dip. Scienze Ginecologiche, Ostetriche e Pediatriche, U.O. Genetica Medica, Pol. S.Orsola-Malpighi, Università di Bologna, Italy
[b] Dip. Biochimica e Biologia Molecolare "E.Quagliariello", Università di Bari, Italy
[c] Dip. Anatomia Patologica, Ospedale Bellaria, Università di Bologna, Italy

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ABSTRACT

Thyroid oncocytic neoplasms are tumors composed of cells characterized by an aberrant increase of mitochondrial mass. They represent a subset of thyroid tumors whose classification and clinical features has been a matter of controversy for clinicians and pathologists alike. The prevalence of oncocytic tumors in the thyroid gland, the relevance of the issues debated, and the obvious cellular derangement of oncocytic cells, namely a complete deregulation of the mitochondrial mass and metabolism, have spurred many investigators to study the molecular mechanism underlying the genesis of this peculiar cancer phenotype. Their findings, which are unraveling the tumor pathobiology, are the subject of the present review.

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1. Introduction

Oncocytic neoplasms are tumors composed of cells characterized by an aberrant amount of mitochondria that is responsible for their 'swollen' (i.e. 'oncocytic', from the Greek word *onkous-tai*, to swell) appearance. These neoplasms are usually benign and may occur at various sites [see (Tallini, 1998) for a review] but are particularly common in the thyroid gland. It is important to note that "oncocytic" change (aberrant increase in the mitochondrial mass) occurs not only in tumors but also in non-neoplastic cells (in this case the terms oncocytic "metaplasia" or "oncocytosis" are often used) and may be associated with ageing, inflammation or hyperplasia (Tallini, 1998). A striking example in the thyroid is Hashimoto's thyroiditis, were lymphocytic infiltration is accompanied by diffuse oncocytic metaplasia of follicular cells. Another example is given by the finding of oncocytic cells in normal parathyroids, where they first appear around puberty and increase in number with ageing, often forming discrete nodules (Tallini, 1998).

Thyroid oncocytic tumors (with the exception of the rare oncocytic variant of medullary carcinoma) originate from follicular cells. They can be benign (oncocytic adenomas) or malignant (oncocytic carcinomas) and have been the subject of both fascination and controversy for clinicians and biologists alike. One area of disagree-

Abbreviations: WHO, World Health Organization; CGH, comparative genomic hybridization; LOH, loss of heterozygosity; FTC, follicular thyroid carcinoma; VHL, Von Hippel Lindau; TCO, Thyroid Tumor with Cell Oxyphilia; NMTCI, Non-Medullary Thyroid Carcinoma I; PTC, papillary thyroid carcinoma; FA, follicular adenoma; HCC, Hurthle cell carcinoma; GTP, guanosintriphosphate; HCA, Hurthle cell adenoma; fNMTC, Familial Non-Medullary Thyroid Carcinoma; LOD, logarithm of odds; OXPHOS, oxidative phosphorylation; mtDNA, mitochondrial DNA; PCR, polymerase chain reaction; miRNA, microRNA.

* Corresponding author at: U.O. Genetica Medica, Policlinico Universitario S.Orsola-Malpighi, Via Massarenti 9, 40138 Bologna, Italy. Tel.: +39 051 2088418; fax: +39 051 2088416.
E-mail address: romeo@eurogene.org (G. Romeo).

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ment has concerned the definition of thyroid oncocytic tumors as a separate tumor category. It is now accepted that oncocytic tumors in the thyroid (as is the case of other organs) should be viewed as special subtypes or variants, since their features are distinct enough to set them apart from corresponding neoplasm lacking accumulation of mitochondria (World Health Organization, 2004). Accordingly, oncocytic thyroid carcinomas are now classified as variants of follicular carcinomas (commonly) or of papillary carcinomas (less commonly).

Oncocytic follicular carcinomas are largely composed of oncocytic cells (>75% of the tumor cells should be oncocytic, according to WHO criteria [World Health Organization, 2004]) and are also known as Hürthle cell tumors, a term that the WHO does not endorse, since it is a misnomer – Hürthle did not describe oncocytic thyroid cells (Tallini, 1998). Oncocytic papillary carcinoma is defined by the presence of both the characteristic changes in nuclear morphology (e.g. grooves, pseudoinclusions) that define papillary carcinoma and the cytoplasmic accumulation of mitochondria that defines oncocytic cells. Tumors described as Warthin-like papillary carcinomas (Apel et al., 1995) are considered oncocytic papillary carcinomas (World Health Organization, 2004). A second area of disagreement concerns the histopathologic definition of malignancy in oncocytic tumors of the thyroid [in the past it was recommended to consider all thyroid oncocytic tumors malignant, see (Tallini, 1998)], and that of their clinical behavior (Stojadinovic et al., 2001). The debate has been fueled by problems in terminology and diagnostic criteria. The issues are particularly relevant for follicular carcinomas, among which the occurrence of diffuse oncocytic modification is generally regarded as an adverse prognostic factor (World Health Organization, 2004). The frequent occurrence of oncocytic tumors in the thyroid gland, the importance of the clinical issues debated, and the striking cellular derangement of oncocytic cells that show complete deregulation of mitochondrial biogenesis, have spurred many investigators to study oncocytic tumors. Their findings, which are now unraveling the tumor pathobiology, are the subject of this review.

2. Chromosomal aberrations and gene defects

No specific pattern of chromosomal aberration has been described for thyroid oncocytic tumors, so that, unlike the case of renal neoplasms, a classification according to large genetic rearrangements is not feasible. Wada et al. (2002) have reported a plethora of chromosomal aberrations in a relatively small set of samples (13 carcinomas and 15 adenomas), involving gains and losses of genetic material from both arms of chromosomes 1, 2, 5, 7, 12, 17, 19, 20 and 22, detected by comparative genomic hybridization (CGH) (Wada et al., 2002). They noticed how gains on chromosome 19p, associated with recurrence of the neoplasia, may suggest an etiological role for chromosome 19 since the same site was reported to contain a locus for a familial form of thyroid oncocytic tumor by linkage analysis (Canzian et al., 1998). They further positively correlated the presence of chromosomal aberration with tumor stage, invasiveness and differentiation degree but cautiously suggested these parameters to be better indicators for prognosis. The same group underlined the similarity of oncocytic tumors with follicular tumors since the latter ones also present a high degree of genetic aberrations (Wada et al., 2002). Grebe et al., on the other hand, reported a frequent LOH on 3p and 17p in a cohort of 14 FTC, 10 of which oncocytic. The rationale of their study was to analyze for LOH regions harboring a known oncogene or tumor suppressor and they particularly focused on *TP53* and *VHL*, since they respectively map on chromosome 17 and 3. Despite the finding that virtually no *TP53* or *VHL* mutations were detected in their relatively small set of samples, the authors suggested that LOH on chromosome 17p may be predictive of outcome, since they positively correlated mortality with occurrence of 17p LOH. The authors also inferred an etiological role for LOH on 10q as an early event in thyroid carcinogenesis, since half FTCs harbored such a genetic defect, confirming the previous observations of Zedenius et al. (Zedenius et al., 1996; Grebe et al., 1997). The studies of Wada et al. confirmed the similar findings of Hemmer et al. (1998), Frisk et al. (1999), Tallini et al. (1999) and Tung et al. (1997) who also inferred an aetiological role for chromosome 2 since in 9/12 tumors they associated LOH on chromosome 2 with oncocytic features. LOH on chromosomes 2q21 and 19p13.2 has been analyzed in a cohort of 70 sporadic oncocytic tumors by our group (Stankov et al., 2004). A statistically significant LOH in the oncocytic sample set with respect to the control set (follicular non-oncocytic tumors) was obtained for the 2q21 region. The number of patients samples showing LOH for the 19p13.2 region did not differ in a statistically significant way from the number of controls. However, LOH was more frequent in oncocytic than in non-oncocytic samples, suggesting that the lack of significance might be due to the relatively small number of cases analyzed. The LOH in the two regions supports the idea that a tumor suppressor gene may be lost in the tumorigenesis process leading to the oncocytic transformation. This hypothesis has been supported also by the finding that, in one affected individual of the large family where the TCO locus has been identified, FISH analysis in the tumor specimen revealed an LOH of the chromosome 19p13.2 region, supporting the linkage data (Canzian et al., 1998). Fig. 1 visually summarizes the chromosomal aberrations reported in thyroid oncocytic tumors.

Several gene rearrangements found in classical PTC/FTC have been reported also in oncocytic tumors, although the prevalence of specific mutations may be different among oncocytic and non-oncocytic thyroid tumors. For example, Nikiforova et al. (2003a) reported *PAX8-PPARγ* rearrangements in follicular tumors but not in follicular tumors with oncocytic change. The *PAX8-PPARγ* gene fusion is the product of a rearrangement bringing in frame the transcription factor PAX8 and the peroxisome proliferator-activated receptor gamma. The authors suggested that this may be a suitable molecular marker to distinguish the two types of tumor. In the same study, they also found that the three forms of oncogenic *RAS* are much less common in oncocytic tumors compared with their non-oncocytic counterparts, leading the group to suggest that different molecular pathways may be involved in the genesis of follicular tumors with and without oncocytic change (Nikiforova et al., 2003a). On the other hand, the works of Cheung et al. (2000) and, subsequently, Chiappetta et al. (2002) have shown that *RET*/*PTC* rearrangement, a marker for papillary thyroid carcinoma, is a common event in oncocytic tumors (even among cases with a follicular growth pattern). *RET*/*PTC*s are chimeric genes generated by the fusion of the *RET* tyrosine kinase domain with the 5′ terminus of other genes, which distinguish the different isoforms detected so far. *RET* is a known proto-oncogene normally inactive in thyroid cells but capable of transformation when activated by ubiquitously expressed genes such as those fused at its 5′ in *RET*/*PTC*s. According to Chiappetta et al. the chimeric oncogene was frequently activated in a cohort of 49 patients, in oncocytic adenomas and carcinomas, but not hyperplastic lesions. Cheung et al. associated the activation of RET/PTC1 (the same variant detected by Chiappetta et al.) with the presence of the nuclear alterations of papillary carcinoma in their oncocytic cases (Cheung et al., 2000). It is possible that in some of these cases RET/PTC may be present in a minority of the neoplastic cells as a result of tumor heterogeneity (Rhoden et al., 2006).

These studies offer an explanation as to why it is often difficult to distinguish histologically benign from malignant forms of