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REVIEW

Tumours of familial origin in the head and neck

Carlos Suárez [a,b], Juan Pablo Rodrigo [a,b], Alfio Ferlito [c,*], Rubén Cabanillas [a,b], Ashok R. Shaha [d], Alessandra Rinaldo [c]

[a] Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
[b] Instituto Universitario de Oncología del Principado de Asturias, Oviedo, Spain
[c] Department of Surgical Sciences, ENT Clinic, University of Udine, I-33100 Udine, Italy
[d] Head and Neck Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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Summary Individuals with inherited cancer syndromes are at significant risk of developing both benign and malignant tumours as a result of a germline mutation in a specific tumour suppressor gene. Tumours of familial origin are a rare event in the head and neck but despite this, they deserve a growing interest. Familial paragangliomas are most of the time limited to the paraganglionar system, but also may be part of different syndromic associations. Since early detection of paragangliomas reduces the incidence of morbidity and mortality, genotypic analysis in the search of SDHB, SDHC and SDHD mutations in families of affected patients plays a front-line diagnostic role, leading to more efficient patient management. Multiple endocrine neoplasia type 1 is characterized by the simultaneous occurrence of at least two of the three main related endocrine tumours: parathyroid, enteropancreatic and anterior pituitary. These tumours arise from inactivating germline mutations in the MEN-1 gene. No clear correlation of MEN-1 genotype with phenotype has emerged to date, and MEN-1 mutation testing in tumours is not used clinically because it has no implications for tumour staging. Multiple endocrine neoplasia type 2 is due to a germline mutation in the RET proto-oncogene. Hallmarks of MEN-2A (the most common phenotypic variant) include medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. The most central clinical difference with MEN-1 is that the associated cancer can be prevented or cured by early thyroidectomy in mutation carriers. Individuals with neurofibromatosis type 1 present early in life with pigmentary abnormalities, skinfold freckling and iris hamartomas, as result of NF1 gene mutation.

Neurofibromatosis type 2 is caused by inactivating mutations of the NF2 gene, and is characterized by the development of nervous system tumours (mainly bilateral vestibular schwannomas), ocular abnormalities, and skin tumours. The molecular genetic basis of nasopharyngeal

* Corresponding author. Tel.: +39 0432 559302; fax: +39 0432 559339.
E-mail address: a.ferlito@uniud.it (A. Ferlito).

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carcinomas remains unknown, but there is evidence for the linkage of these tumours to chromosome 3p. Finally, the high rate of p16 mutations in squamous cell carcinomas and the association of p16 with familial melanoma propose p16 as an ideal candidate gene predisposing to familial squamous cell carcinomas. The elucidation of the cellular processes affected by dysfunction in familial tumours of the head and neck may serve to identify potential targets for future therapeutic interventions.

Introduction

Individuals with inherited cancer syndromes are at significant risk of developing both benign and malignant tumours as a result of starting life with a germline (inherited) mutation in one of the two copies of a specific tumour suppressor gene. Since affected individuals are heterozygous for a loss of function mutation in one copy of a tumour suppressor gene, only one additional genetic alteration (loss of the wild-type allele) is needed to facilitate tumour development. This two-step process of tumour suppressor gene inactivation was coined the 'two-hit hypothesis' by Alfred Knudson[1] in his classic monograph on retinoblastoma. In this fashion, a cell that undergoes inactivation of both copies of a specific tumour suppressor gene has an increased growth advantage relative to cells with wild-type tumour suppressor gene function.

The proteins encoded by tumour suppressor genes mutated in cancer predisposition syndromes are growth regulators critical for the maintenance of orderly cell growth and differentiation. A simplified view of tumour suppressor gene function envisions three main intracellular compartments important for regulating cell proliferation and survival, including: (i) the cell membrane where cues from the environment are transduced to the interior of the cell; (ii) the cytoplasm, where these extracellular signals are transmitted to the nucleus; and (iii) the nucleus, where cell cycle regulation dictates whether a cell will initiate DNA synthesis and undergo mitosis. Dysregulated function of proteins in any of these three compartments can result in an increased growth advantage and can, by itself, predispose the cell to transformation or do so in concert with other genetic changes. The identification of tumour suppressors mutated in specific inherited cancer syndromes allows us to pinpoint critical signal transduction pathways, cell cycle regulatory events and extracellular cues that instruct a particular cell type to proliferate or differentiate. The elucidation of the cellular processes affected by dysfunction of these molecules may serve to identify potential targets for future therapeutic interventions.

Familial paragangliomas

Epidemiological and clinical aspects

Paragangliomas (PGLs) are neoplasms of neuroectodermal origin, embryologically derived from the neural crest cells, which originate in the paraganglia, a collection of small neuroendocrine organs that are distributed throughout the body, from the middle ear and the skull base to the pelvic floor. These tumours are usually divided into two categories, those developing in the head and neck region and those arising elsewhere, with the adrenal medulla being the major site. Adrenal PGLs are usually referred to as pheochromocytomas.

Head and neck PGLs are relatively uncommon tumours, representing 0.012% of all human tumours and 0.6% of all neoplasms in the head and neck. Carotid body neoplasms account for about 60% of head and neck PGLs and are situated at the bifurcation of the common carotid artery within the adventitia. The middle ear is the next most common site of head and neck PGLs. Jugular tumours located in the region of the jugular foramen commonly traverse the skull base to be located both intra- and extra-cranially and within the jugular vein. Vagal PGLs account for less than 5% of all head and neck PGLs. Other sites of paraganglionic tissue within the head and neck where tumours may rarely arise include: the nasopharynx, nasal cavities, paranasal sinuses, larynx, thyroid gland and orbit.[2] It is estimated that up to 40% of the head and neck PGLs reported in the literature are familial, which corresponds to one of the highest frequencies among human tumours,[3] and up to 10% are false sporadic tumours.[4]

Although most of the sporadic head and neck PGLs present as a single mass, multicentric or bilateral tumours can occur in 10% of the cases. In the familial setting about 30—40% of the patients have multicentric PGLs, that may also develop at other sites of the head and neck region or at the sympathoadrenal abdominal paraganglia. Despite head and neck PGLs are non-secreting tumours of parasympathetic origin, about 3% of them demonstrate clinical evidence of hyperfunctioning.[5]

The malignant potential of PGLs reported in the literature varies greatly; it appears as though PGLs arising in the vicinity of the organ of Zuckerkandl have the highest malignant potential (14—50%).[6,7] In the head and neck region, vagal PGLs are considered the PGLs with the greatest propensity for malignant behaviour. The incidence of metastasis generally is estimated to be approximately 10%, but has been reported to be as high as 19%.[5] The observed incidence of malignancy for jugulotympanic PGLs and carotid body PGLs is 5.1% and 1.41%, respectively.[8] The high rate of malignant PGLs of the larynx reported in the literature (25%) is attributable to cases of neuroendocrine carcinomas, especially atypical carcinoid, which may have been misdiagnosed as PGLs. Critical reviews of the literature have accepted only one case of metastatic PGL of the larynx.[9,10] The frequency of malignant PGL of the sinonasal region is 24% giving a higher rate of malignancy in the head and neck area. This percentage includes metastasis and/or intracranial extension of the neoplasm.[8]