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Review

Models of parent-of-origin tumorigenesis in hereditary paraganglioma

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ABSTRACT

Paraganglioma and pheochromocytoma are neuroendocrine tumors that originate from either the sympathetic or the parasympathetic branches of the autonomic nervous system. Although 14 different genes have been linked to paraganglioma/pheochromocytoma, a subgroup of these genes is associated with hereditary paraganglioma–pheochromocytoma, the genes related to mitochondrial succinate dehydrogenase (SDH) including *SDHA*, *SDHB*, *SDHC*, *SDHD* and the assembly factor *SDHAF2*. Unlike mutations in other *SDH* subunit genes, mutations in *SDHD* and *SDHAF2* show a remarkable parent-of-origin dependent tumorigenesis in which tumor formation almost exclusively occurs following paternal transmission of the mutation. To date, three different models have sought to explain the striking inheritance pattern seen in *SDHD* and *SDHAF2*-linked families. Despite the fact that the models suffer to varying degrees from a lack of experimental verification, all three models have made some attempt to incorporate current data and understanding of this phenomenon. In this review, we discuss our present understanding of this phenomenon and describe the three models that seek to explain the inheritance pattern in *SDHD* and *SDHAF2*-linked families.

Contents

1. Introduction

The neuroendocrine tumor, paraganglioma, is associated with both the sympathetic and parasympathetic nervous systems. Pheochromocytomas are closely related neuroendocrine tumors but are exclusively associated with the sympathetic nervous system. Parasympathetic paragangliomas occur most commonly in the head and neck region and most frequently arise in the carotid body at the bifurcation of the carotid artery, while pheochromocytomas arise in the adrenal medulla and sympathetic paragangliomas occur elsewhere in the abdomen and thorax [1]. Paragangliomas of the head and neck usually show relatively mild symptoms and display a characteristically indolent tumor progression [2]. Prominent characteristics of pheochromocytomas and extra-adrenal

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paragangliomas are the hypersecretion of catecholamines and elevated blood pressure. Sympathetic paragangliomas also show a greater propensity for malignant degeneration compared to pheochromocytomas or head and neck paragangliomas [3].

2. Associated genes

Paraganglioma–pheochromocytoma is associated with a heterogeneous collection of genes, with germline or somatic mutations identified in 14 genes to date. These genes belong to a wide range of functional categories that include kinase receptors (RET), regulators of signaling (NF1, HRAS), hypoxia-related factors (VHL, HIF2A), enzymes involved in energy metabolism (SDHA, SDHB, SDHC, SDHD, SDHAF2, FH, MDH2), endosomal signaling factors (TMEM127), vesicle transport/apoptosis (KIF1B), and transcription factors (MAX) [4,5].

Although germline mutations in most of these genes lead to autosomal dominant inheritance patterns of the disease in families, there are several prominent exceptions: *SDHD*, *SDHAF2* and *MAX*. The *SDHD* and *SDHAF2* genes both encode proteins related to the mitochondrial succinate dehydrogenase (SDH) complex and tumor development occurs almost exclusively in carriers of paternal mutations [6,7]. Carriers of MAX mutations also show 'paternal-only' tumor development, but in contrast to the so-called cluster 1 pseudohypoxia-driven tumors including the SDH genes and VHL, MAX mutations are associated with cluster 2, the PGL/PCC subgroup thought to be associated with kinase signaling [5,8].

3. Succinate dehydrogenase

Mutations in succinate dehydrogenase (SDH) complex genes (*SDHA*, chromosome 5p15; *SDHB*, chromosome 1p36; *SDHC*, chromosome 1q23; *SDHD*, chromosome 11q23; and *SDHAF2*, chromosome 11q12) are associated with head and neck paragangliomas, extra-adrenal paragangliomas, and pheochromocytomas [6,9–12]. *SDHD* encodes one of the two membrane-anchoring subunits, while *SDHAF2* encodes an accessory factor involved in complex assembly. The SDH genes act as tumor suppressors and all appear to follow the Knudson model, showing loss of heterozygosity (LOH) in conjunction with a germline mutation. This results in loss of a protein subunit, which in turn destabilizes the SDH complex as a whole and abolishes enzymatic activity [13]. The catalytic subunit consists of two soluble proteins, a flavoprotein (encoded by *SDHA*) and an iron–sulfur protein (*SDHB*), while subunits encoded by *SDHC* and *SDHD* anchor the complex in the inner mitochondrial membrane and bind ubiquinone.

SDH, also known as succinate–coenzyme Q reductase, has a dual function as an enzyme of the mitochondrial tricarboxylic acid cycle and as complex II of the electron transport chain. In the former role it oxidizes succinate to fumarate, while in the latter it reduces ubiquinone to ubiquinol, contributing to the generation of ATP by oxidative phosphorylation. SDH inactivation induces an accumulation of succinate [14–16] or the generation of reactive oxygen species (ROS) [17–23], leading to inhibition of α-ketoglutarate-dependent HIF prolyl hydroxylases and the activation of hypoxia inducible factor (HIF).

Despite the close functional relationship of the SDH proteins, mutations result in striking differences in both tumor location and clinical phenotype. The molecular basis for this clinical divergence is not yet understood.

SDHAF2 encodes a gene for a novel protein that acts as an accessory/assembly factor for the SDH complex, adding a flavin-adenine dinucleotide (FAD) prosthetic group to form a catalytically active SDHA flavoprotein. Initially referred to as SDH5, the succinate dehydrogenase complex assembly factor 2 (SDHAF2) was shown to be essential for the correct flavination of SDHA and function of the SDH complex. The first mutation identified in *SDHAF2*, a missense variant c.232G>A (p.Gly78Arg), was identified in a large Dutch head and neck paraganglioma kindred and was shown to result in the loss of SDHA flavination and activity of the SDH complex [6].

A follow-up study in 443 paraganglioma and pheochromocytoma patients found no further mutations and demonstrated that *SDHAF2* mutations make a very modest contribution to the overall genetic burden in these syndromes [24]. A notable characteristic of *SDHAF2* mutations is the very high penetrance (i.e., the chance that a mutation carrier will develop a tumor). Of the known mutation carriers in the main Dutch kindred, all unaffected individuals are currently under the age of 45. This high level of penetrance is reminiscent of SDHD, which also shows very high penetrance compared to the other SDH genes.

4. MAX

MAX (chromosome 14q23) is a basic helix-loop-helix transcription factor that forms a complex with the important oncogene MYC. MAX is also found in repressor complexes with other transcription factors, which effectively oppose the function of the MYC-MAX heterodimer [25]. Germline loss-of-function *MAX* mutations were identified by sequencing the entire exome of 3 unrelated patients with a family history of pheochromocytoma [8]. Intriguingly, these patients exhibited a loss of heterozygosity of the wild-type allele that was shown to be dependent on uniparental disomy (in this case duplication of the paternal chromosome). An additional 5 cases were identified in a follow-up study [8] and in a study of 1694 pheochromocytoma and paraganglioma patients negative for mutations in other known genes, Burnichon et al. showed that germline mutations in *MAX* were responsible for 1.1% of cases [26]. Although the total number of patients identified is still limited, these studies showed exclusively paternal transmission of *MAX* mutations in affected patients, with tumor formation absent in individuals with maternally inherited mutations. Furthermore, it was shown that *MAX* is not imprinted [8]. Although at present there is no explanation for the pattern of inheritance, it is worth noting that chromosome 14 harbors several imprinted genes. It is possible that loss of the maternally expressed gene 3 (MEG3), an imprinted non-coding RNA gene silenced on the paternal allele, plays a role in *MAX* tumor development. In accordance with the Knudson model, loss of *MAX* (and perhaps also *MEG3*) due to uniparental paternal disomy affecting chromosome 14q is the prelude to tumor formation [8]. Alternatively, it is also possible that overexpression of a paternally expressed imprinted gene on chromosome 14 such as RTL1 [27] is essential for tumorigenesis, or that chromosomal duplication in the tumor is required to delete wild-type *MAX* while maintaining sufficient expression of an unknown haploinsufficient gene, loss of which would otherwise limit growth of tumor cells.

5. Inheritance pattern

In the late 1980s, Dr. Andel van der Mey and colleagues at Leiden University Medical Center noticed an unusual pattern of tumor inheritance in families with paraganglioma type 1 (PGL1), with an apparently exclusive development of tumors in the children of male family members [7]. Clinicians and scientists working at Leiden University Medical Center were well-placed to recognize the paternal inheritance of PGL1 tumor susceptibility due to the predominance of PGL1-linked cases, and absence of cases linked to other genes, amongst the numerous affected families in the immediate Leiden area. In a second area of the Netherlands, the Nijmegen/Den Bosch region, researchers from the Radboud

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