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Succinate dehydrogenase (*SDHx*) mutations in pituitary tumors: could this be a new role for mitochondrial complex II and/or Krebs cycle defects?

Paraskevi Xekouki and **Constantine A Stratakis**
Section on Endocrinology and Genetics (SEGEN), Program on Developmental Endocrinology and Genetics (PDEGEN), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Inter-Institute Pediatric Endocrinology Program, National Institutes of Health (NIH), Building 10, CRC, Room 1-3330, 10 Center Drive, MSC1103, Bethesda, Maryland 20892, USA

Abstract

Succinate dehydrogenase (SDH) or mitochondrial complex II is a multimeric enzyme that is bound to the inner membrane of mitochondria and has a dual role as it serves both as a critical step of the tricarboxylic acid or Krebs cycle and as a member of the respiratory chain that transfers electrons directly to the ubiquinone pool. Mutations in SDH subunits have been implicated in the formation of familial paragangliomas (PGLs) and/or pheochromocytomas (PHEOs) and in Carney–Stratakis syndrome. More recently, SDH defects were associated with predisposition to a Cowden disease phenotype, renal, and thyroid cancer. We recently described a kindred with the coexistence of familial PGLs and an aggressive GH-secreting pituitary adenoma, harboring an *SDHD* mutation. The pituitary tumor showed loss of heterozygosity at the *SDHD* locus, indicating the possibility that *SDHD*'s loss was causatively linked to the development of the neoplasm. In total, 29 cases of pituitary adenomas presenting in association with PHEOs and/or extra-adrenal PGLs have been reported in the literature since 1952. Although a number of other genetic defects are possible in these cases, we speculate that the association of PHEOs and/or PGLs with pituitary tumors is a new syndromic association and a novel phenotype for SDH defects.

Introduction

Succinate dehydrogenase (SDH) or succinate-coenzyme Q reductase is a multimeric enzyme that is bound to the inner membrane of mitochondria (Oyedotun & Lemire 2004). It has a dual role as it serves both as a critical step of the tricarboxylic acid (TCA) or Krebs cycle and as a member of oxidative phosphorylation, the respiratory chain that transfers electrons directly to the ubiquinone pool (Kantorovich & Pacak 2010). It is a highly conserved protein complex that consists of four subunits: two hydrophilic, a flavoprotein (SDHA) and an iron–sulfur protein (SDHB) that together form the catalytic core of the enzyme (SDHA serves as the substrate binding site for succinate), and two hydrophobic subunits, SDHC and SDHD, that anchor the holotetramer to the membrane and serve as the ubiquinone site (Oyedotun & Lemire 2004, Kantorovich & Pacak 2010).

Correspondence should be addressed to: C A Stratakis; stratakc@mail.nih.gov.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Syndromes related to SDHx mutations

The discovery that mutations in genes coding for the subunits *SDHB*, *SDHC*, and *SDHD* were responsible for the formation of multiple and possibly coexisting parasympathetic and sympathetic paragangliomas (PGLs) and/or pheochromocytomas (PHEOs) (Baysal *et al.* 2000, Astuti *et al.* 2001) made obsolete (Dluhy 2002) at least one part of the axiom that had been proposed by Bravo & Gifford (1984); the so-called '10 rule' had stated that 10% of PHEOs were bilateral, 10% malignant, 10% normotensive, 10% extra-adrenal, and 10% genetic origin. Today, we know that as many as 40% of PHEOs/PGLs may be due to a genetic defect (Raygada *et al.* 2011); in children and young adults, this may be true in as many as three out of four patients.

In 2007, Stratakis *et al.* described germline mutations of the *SDHB*, *SDHC*, and *SDHD* genes in patients with PGLs and gastrointestinal stromal tumors (GISTs), negative for mutations in *PDGFRA* or *KIT* genes (McWhinney *et al.* 2007). GISTs from these patients showed allelic losses of the *SDHB* and *SDHC* chromosomal loci pointing to a tumor-suppressor function of SDH subunits (SDHx) in these neoplasms. This was the first time that a germline mitochondrial oxidation defect was linked to predisposition for development of a sarcoma. More recently, *SDHx* mutations (or functional variants) were associated with predisposition to a Cowden disease-like phenotype that consisted of breast, endometrial, thyroid, kidney, colorectal cancers, dermatological features such as oral and skin papillomas, and neurological manifestations such as autism and Lhermitte Duclos disease (Ni *et al.* 2008), as well as with renal and thyroid cancer (Neumann *et al.* 2004, Vanharanta *et al.* 2004).

Pituitary adenomas and PHEOs/PGLs as part of multiple endocrine neoplasia syndromes

Pituitary adenomas represent one of the components of multiple endocrine neoplasia type 1 (MEN1) due to mutations in *MEN1* gene, the other components being primary hyperparathyroidism and pancreatic tumors. Adenomas and adenomatous hyperplasia of the thyroid and adrenal glands may also occur in patients with MEN1 (Thakker 2010).

PHEOs/PGLs, primary hyperparathyroidism, and medullary thyroid cancer are the main tumors that occur in multiple endocrine neoplasia type 2 (MEN2), with particular marfanoid habitus in MEN2B subtype. The genetic causes are gain-of-function mutations in *RET* proto-oncogene (Wohllk *et al.* 2010).

There have been some reports in the literature of MEN1 where PHEOs (unilaterally or bilaterally) were identified in patients with proven *MEN1* mutations. However, the prevalence of PHEOs in MEN1 appears to be < 0.1% (Gatta-Cherifi *et al.* 2012).

We just described a kindred with the coexistence of familial PGLs and an aggressive GH-secreting pituitary adenoma, harboring a *SDHD* mutation (Xekouki *et al.* 2012). The pituitary tumor showed loss of heterozygosity (LOH) at the *SDHD* locus, indicating the possibility that this gene's loss was causatively linked to the development of the neoplasm (Xekouki *et al.* 2012). Until this report, coexistence of a pituitary adenoma and PHEOs/PGL was not recognized as a distinct entity. However, since 1952, we have identified 29 cases in the literature of pituitary adenomas copresenting with PHEO and/or extra-adrenal PGLs (Table 1); in most reports, the coexistence of these two tumors was described as a unexpected 'coincidence'. Unfortunately, no genetic testing was available until the 1990's, so we can only hypothesize that some of the early cases presented in Table 1 could represent cases of MEN syndromes or may be due to *SDHx* mutations. The most recent cases

described by Sisson *et al.* (2011) and Zhang *et al.* (2011) have a lot of similarities with our case and most probably are cases of familial PGLs.

The only other reported patient with a pituitary tumor and neck PGLs due to an *SDHC* splice site mutation is the one reported by López-Jiménez *et al.* (2008). However, the prolactinoma could not be tested for LOH, so we can only speculate that this particular mutation may have contributed to the patient's pituitary tumor formation.

Proposed mechanisms

The above data and the number of cases in Table 1 indicate that the association of certain pituitary tumors and SDHx mutations may be a real one, adding this neoplasm to the ever increasing list of lesions associated with SDH deficiency. How could this be molecularly plausible? Several mechanisms have been proposed to explain how the dysfunction of SDHx can lead to the formation of PHEOs/PGLs. The first model is 'pseudohypoxia' and accumulation of reactive oxygen species (ROS). In normoxic conditions, a family of oxygen-dependent enzymes known as prolyl hydroxylases (PHD) 1, 2, and 3 (also known as *Egln2*, *Egln1*, and *Egln3*) hydroxylate the three α subunits of hypoxia inducible factor α (HIF1α, HIF2α, and HIF3α). The hydroxylated HIFαs are then targeted by von Hippel–Lindau (VHL) protein, an E3 ubiquitin ligase, polyubiquitinated and degraded in the proteasome. Only hydroxylated HIFαs can be targeted by VHL for degradation. However, if PHDs are inhibited by the accumulated succinate (such as when SDHx are mutated), HIFαs are not hydroxylated, escape degradation, and translocate to the nucleus, where they dimerise with HIF1β and bind to specific promoter elements of target genes including critical angiogenic factors such as vascular endothelial growth factor (VEGF), enzymes involved in glucose metabolism, and cell survival, and possibly a number of others (Raimundo *et al.* 2011; Fig. 1a). Activation of the HIF pathway and the resulting angiogenic and glycolytic response in SDHx-mutated tumors was first reported by Selak *et al.* (2005) and has been replicated in many studies. Certainly, the 'pseudohypoxia' hypothesis is not new: Otto Warburg in the 1920s described a striking rate of glycolysis and lactate production in tumor cells, in the presence of normal oxygen concentrations (Warburg 1956). Warburg proposed that this phenomenon might be related to a defect in mitochondrial respiration, or some other mechanism that allows the tumor cell to function as hypoxic under normoxic conditions. It took over 80 years for the 'Warburg effect' to be confirmed, and today, it is the basis for the use of functional imaging strategies such as the [^{18}F]deoxyglucose-positron emission tomography (^{18}F-FDG PET) for the diagnosis of PHEO/PGLs (Bayley & Devilee 2010). The generation of ROS due to the SDH/complex II deficiency in the presence of SDHx mutations has also been implicated in tumor formation, although ROS are usually a 'by-product' of other elements of the electron transport chain, particularly complex I (NADH-ubiquinone oxidoreductase) and III (ubiquinone-cytochrome *c* oxidoreductase). ROS might promote tumor formation in SDH-deficient cells by inhibiting PHD activity similar to succinate accumulation (Bardella *et al.* 2011; Fig. 1b). The accumulation of succinate in SDH-deficient tumors may also inhibit other components of α-ketoglutarate-dependent enzymes besides PHDs. It was recently demonstrated that loss of SDHB subunit in a yeast model led to succinate accumulation, which could cause the inhibition of two different α-ketoglutarate-dependent dioxygenases: the Jlp1, involved in sulfur metabolism, and the histone demethylases Jhd1, which belongs to the JmjC-domain-containing histone demethylase (JHDM) enzymes. It was also demonstrated that JMJD2D, the corresponding human JHDM, was inhibited by succinate accumulation (Smith *et al.* 2007). Inhibition of the histone demethylases could certainly lead to tumor formation by a variety of epigenetic changes (Bardella *et al.* 2011). Indeed, increased methylation of histone H3 that can be reversed by overexpression of the JMJD3 histone demethylase was recently reported in *SDHB*-silenced cells (Fig. 2). ChIP analysis revealed that the core promoter of

IGFBP7, which encodes a secreted protein upregulated after the loss of SDHB, showed decreased occupancy by trimethylated lysine 27 on histone H3 (H3K27me3) in the absence of SDHB. Moreover, type I chief cells, which are considered the neoplastic component of PGLs, were shown as the major methylated histone-immunoreactive component of the paraganglial carotid tumors tested (Cervera *et al.* 2009). Overall, these findings demonstrated that succinate could act not only as a messenger between mitochondria to cytosol but also as a signal between mitochondria to nucleus, for the regulation of chromatin structure and gene expression.

Conclusions

Could all of this be happening in the pituitary as well? The mechanism by which *SDHx* germline mutations might contribute to pituitary tumor formation is still elusive. In our studies, we showed increased expression of HIF1α in the *SDHD*-mutant tumor cells compared with normal pituitary and GH-secreting adenoma cells without SDH defects (Xekouki *et al.* 2012). Clearly, further research is needed to prove SDHx mutation involvement in predisposition to pituitary tumors; however, the clinical cases and the preliminary laboratory data make this enzyme a likely candidate for yet another molecular mechanism through which pituitary tumors may form.

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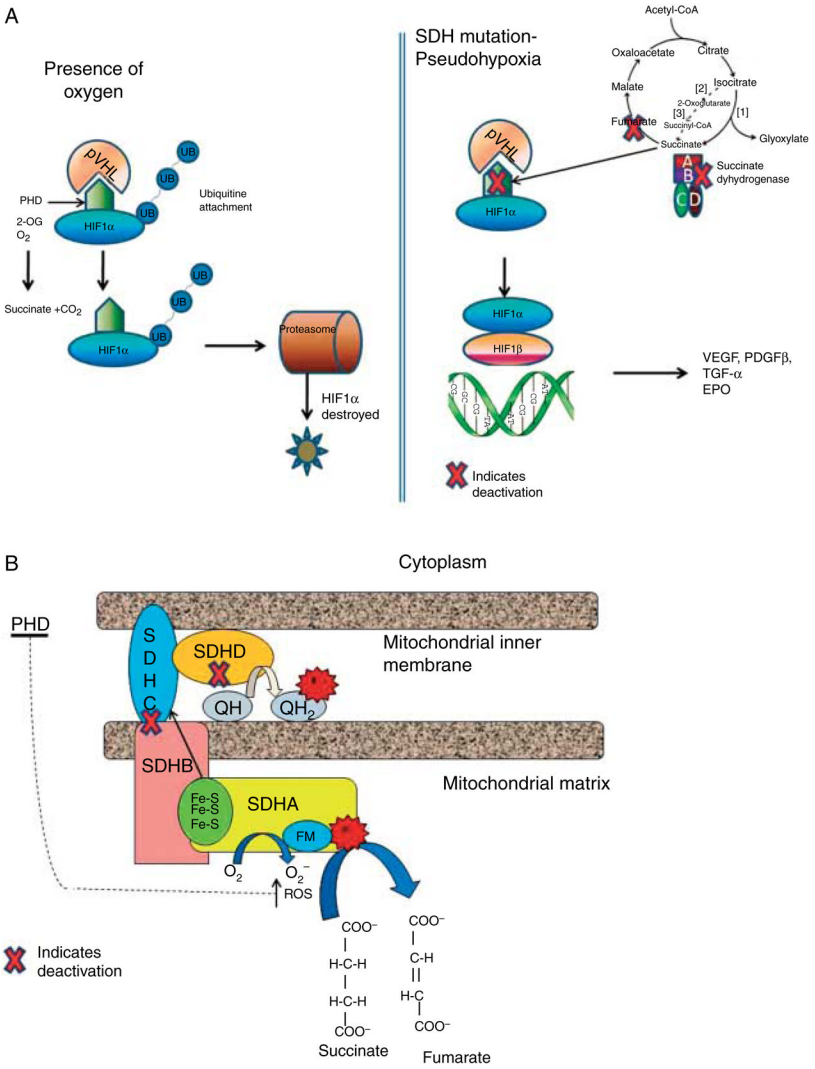

Figure 1.

(a) Mechanisms of pseudohypoxia in inherited PHEO and/or PGLs: inactivation of SDH leads to the abnormal stabilization of HIFs in normoxia that escape degradation and translocate to the nucleus, where they dimerise with HIF1β and promote transcription of genes that enhance tumorigenesis, e.g. VEGF, PDGF-β (2-OG, a-ketoglutarate; HIFs, hypoxia-inducible factors; PHD, prolyl hydroxylases; SDH, succinate dehydrogenase; VHL, Von Hippel–Lindau). (b) Oxidation of succinate to fumarate transfers the electrons through a sequence of steps from the flavin moiety in SdhA to a set of three iron–sulfur clusters in SdhB, to the ubiquinone binding site in SdhC and SdhD. When complex II is disrupted due to mutations in SdhB, SdhC, or SdhD, the electron transfer is impaired promoting superoxide generation through the autoxidation of the reduced flavin group by O_2 in the matrix (FM, flavin moiety; Fe-S, iron–sulfur clusters; e^-, electron transfer; QH, ubiquinone; QH_2, ubiquinol).

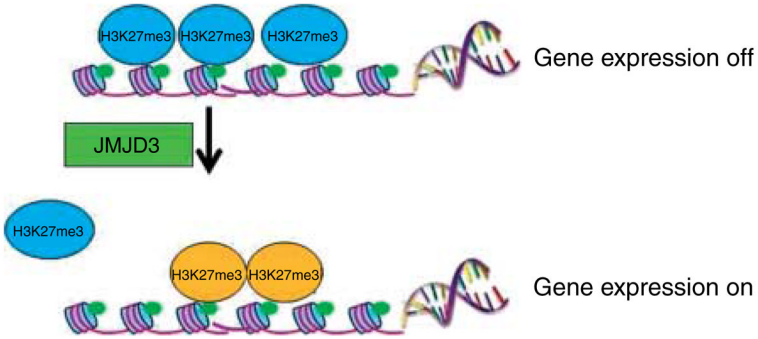

Figure 2.
Methylation of histones like trimethylated lysine 27 on histone H3 (H3K27me3) controls transcription by allowing chromosomal regions to alternate between ‘on’ and ‘off’. Jumonji domain-containing 3 (JMJD3) belongs to a family of enzymes that uses a Jumonji C (JmjC) domain to catalyze demethylation on lysines. In cells with inactivated *SDHB*, increased methylation of histone H3 can be reversed by overexpression of the JMJD3, indicating that histone demethylases may be involved in the formation of paragangliomas (and related tumors).

Table 1

Reported cases of coexistence of PHEO/PGL and pituitary adenoma

Report	Age[a]/sex	Case	Genetic screening	Family history for endocrine tumors	Comments
Iversen (1952)	44/M	Acromegaly/PHEO	_[b]	NA	
Kahn & Mullon (1964)	40/M	Acromegaly/PHEO	_[b]	NA	
O'Higgins *et al.* (1967)	21/F	Acromegaly/PHEO increased serum calcium (PHP?)	_[b]	NA	
Steiner *et al.* (1968)	41/M	Cushing's disease/bilateral PHEOs/medullary thyroid cancer	_[b]	Positive for MEN for VI generations	
Wolf *et al.* (1972)	43/F	Pituitary adenoma (probably nonfunctioning), PHEO/PHP, medullary thyroid cancer	_[b]	NA	
Farhi *et al.* (1976)	19/F	Acromegaly/PGLs/, parathyroid hyperplasia, pigmentary abnormalities	_[b]	Negative	
Kadowaki *et al.* (1976)	44/M	Acromegaly/PHEO	_[b]	NA	
Osamura *et al.* (1977)	58/M	Acromegaly/PHEO/renal carcinoma	_[b]	NA	
Manger *et al.* (1977)	15/F	Acromegaly/PHEO	_[b]	NA	
Melicow (1977)	52/F	Chromophobe adenoma of pituitary/papillary carcinoma of thyroid/PHEO diagnosed postmortem	_[b]	NA	
Janson *et al.* (1978)	28/F	Pituitary adenoma (probably nonfunctioning) /bilateral PHEO	_[b]	Positive for PHEOs/ islet cell tumor/ renal adenoma	
Alberts *et al.* (1980)	36/F	Pituitary adenoma (?)/PHEO/islet cell tumor (gastrinoma), Cushing's syndrome (adrenal cortical adenoma), parathyroid hyperplasia	_[b]	NA	
Myers & Eversman (1981)	53/F	Acromegaly/PHEO/PHP	_[b]	Negative	
Anderson *et al.* (1981)	53/F	Acromegaly/PHEO/ parathyroid hyperplasia (diagnosed post-mortem)	_[b]	Negative	
Anderson *et al.* (1981)	58/F	Acromegaly/PHEO	_[b]	Negative	Hypertension in one sibling (PHEO?)
Meyers (1982)	35/F	Prolactinoma/PHEO	_[b]	NA	
Roth *et al.* (1986)	43/M	Acromegaly (nodular somatotroph hyperplasia)/PHEO	_[b]	Negative	Ectopic GHRH secretion from PHEO
Bertrand *et al.* (1987)	26/M	Prolactinoma/PHEO/bilateral medullary thyroid carcinoma (MTC), parathyroid adenoma	_[b]	Father: metastatic MTC/ probably PHEO	
Teh *et al.* (1996)	41/M	Acromegaly/PHEO/abdominal PGL	*RET*: (−)	NA	

Report	Age[a]/sex	Case	Genetic screening	Family history for endocrine tumors	Comments
Baughan *et al.* (2001)	43/M	Acromegaly/PHEO/hemangioma/lipoma/parotid adenoma	*RET*: (−)	Negative	Maybe ectopic GHRH secretion (not measured)
Dünser *et al.* (2002)	56/M	Pituitary adenoma (probably not secreting) /PHEO	Not performed	NA	
Sleilati *et al.* (2002)	57/F	Acromegaly/PHEO	*RET*: negative	Negative	Negative for GHRH ectopic secretion
Breckenridge *et al.* (2003)	59/M	Pituitary adenoma (non- secreting)/PHEO	Not performed	Negative	
López-Jiménez *et al.* (2008)	60/M	Prolactinoma/nonsecreting PGL	*SDHC* (+)	2/4 children are carriers of the same mutation. Parents' history: negative	
Saito *et al.* (2010)	40/M	Acromegaly/MTC	*RET* (+)	Mother PHEO/MTC *RET* (+)	
Zhang *et al.* (2011)	45/M	Acromegaly/PGLs	Not performed	Father and sister neck PGLs	
Heinlen *et al.* (2011)	60/M	PHEO/nonsecreting pituitary adenoma/MTC	*RET* (+)	NA	
Sisson *et al.* (2011)	29/M	Bilateral PHEOs/ acromegaly/PTC	Not performed	Negative	
Xekouki *et al.* (2012)	37/M	Acromegaly/bilateral PHEOS/PGLs	*SDHD* (+) LOH of *SDHD* locus in pituitary adenoma	Sister, paternal uncle: neck PGLs (same mutation)	

NA, not available; PHEO, pheochromocytoma; PGL, paraganglioma; PTC, papillary thyroid cancer; MTC, medullary thyroid cancer; PHP, primary hyperparathyroidism; MEN, multiple endocrine neoplasia; M, male; F, female.

[a]The age at first visit.

[b]DNA testing was not available at that time.