Biochimica et Biophysica Acta 1827 (2013) 573–577

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

Mitochondrial complex II and genomic imprinting in inheritance of paraganglioma tumors☆

Bora E. Baysal *

Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY, 14263, USA

ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form 17 December 2012
Accepted 19 December 2012
Available online 2 January 2013

Keywords:
Mitochondrial complex II
Succinate dehydrogenase
Paraganglioma
Imprinting
SDHD

ABSTRACT

Germ line heterozygous mutations in the structural subunit genes of mitochondrial complex II (succinate dehydrogenase; SDH) and the regulatory gene *SDHAF2* predispose to paraganglioma tumors which show constitutive activation of hypoxia inducible pathways. Mutations in *SDHD* and *SDHAF2* cause highly penetrant multifocal tumor development after a paternal transmission, whereas maternal transmission rarely, if ever, leads to tumor development. This transmission pattern is consistent with genomic imprinting. Recent molecular evidence supports a model for tissue-specific imprinted regulation of the *SDHD* gene by a long range epigenetic mechanism. In addition, there is evidence of *SDHB* mRNA editing in peripheral blood mononuclear cells and long-term balancing selection operating on the *SDHA* gene. Regulation of SDH subunit expression by diverse epigenetic mechanisms implicates a crucial dosage-dependent role for SDH in oxygen homeostasis. This article is part of a Special Issue entitled: Respiratory complex II: Role in cellular physiology and disease.

1. Introduction

Identification of germ line heterozygous mutations in SDH genes in hereditary paraganglioma and pheochromocytoma (PGL/PHEO) families highlighted an essential role for mitochondria in tumor suppression [1–4]. Mutations in the mitochondrial complex II structural subunit genes *SDHB*, *SDHC* and *SDHD* and the regulatory subunit gene *SDHAF2* were described in many PGL families. *SDHB* encodes the hydrophilic catalytical iron–sulfur-containing subunit. *SDHC* and *SDHD* encode the two hydrophobic subunits that span the inner mitochondrial membrane and sandwich a single heme moiety [5]. *SDHAF2* is a recently characterized regulatory subunit essential for flavination of the major catalytical subunit encoded by *SDHA* [4]. Mutations in *SDHA* were described in several isolated but not in familial paraganglioma cases [6,7]. PGL tumors derive from paraganglia, highly specialized small neuroendocrine organs and clusters of tissues located internally near large vessels and nerves [8]. Carotid body, a small oxygen-sensing organ located at the bifurcation of the common carotid artery in the neck and adrenal medulla, located inside of the adrenal glands in the retroperitoneum above the kidneys is the most prominent paraganglionic organ. Large-scale mutation analyses of isolated PGL and PHEO (a hormone secreting type of paraganglioma located in adrenal medulla) cases uncovered a high incidence of occult germ line mutations in SDH genes [9]. Clinical aspects of PGL/PHEO, including mutation detection, imaging and treatment have been reviewed recently [10]. Here, the focus will be on the evidence for epigenetic regulation of SDH subunits.

2. Imprinted transmission of *SDHD* and *SDHAF2* mutations

First evidence of imprinted transmission of *SDHD* mutations was described in 1989 [11], even before the gene location (PGL1 locus) was pinpointed by linkage analysis to chromosome band 11q23 in extensive multigenerational Dutch pedigrees [12]. Genetic analyses showed that paraganglioma tumors developed only if the mutation was transmitted by a father. No evidence of tumor development was seen upon maternal transmission of mutation. The parent-of-origin effect was overwhelmingly confirmed in other PGL1 families before discovery of the underlying gene, *SDHD* [13,14]. Interestingly, a distinct paraganglioma locus named *PGL2* which was mapped to chromosome 11q13 in other Dutch families also showed a similar pattern of parent-of-origin effect: the tumors developed only after a paternal mutation transmission [15]. The *PGL2* locus was recently identified as the *SDHAF2* gene by discovery of a single recurrent mutation resulting in Gly-to-Arg substitution at codon 78 [4]. Recent investigation of an extended *PGL2* family confirms that tumor development occurs exclusively after paternal transmission of *SDHAF2* mutations consistent with genomic imprinting [16]. Notably, the mutations in *SDHB* and *SDHC*, located on chromosome bands 1p51 and 1q23, respectively, do not show evidence of imprinted transmission because either maternal or paternal transmission of mutations causes tumor development.

Abbreviations: PGL, Hereditary paraganglioma; PHEO, Pheochromocytoma; SDHAF2, succinate dehydrogenase complex assembly factor 2; CTCF, CCCTC-binding factor (zinc finger protein); LOH, Loss of heterozygosity; Linc RNA, large intergenic non-coding RNA; UPGL, Untranslated RNA in PGL locus (lincRNA at boundary of *SDHD* locus); ROS, reactive oxygen species; Bp and kb, base pair and kilobase

☆ This article is part of a Special Issue entitled: Respiratory complex II: Role in cellular physiology and disease.

* Tel.: +1 716 845 3204; fax: +1 716 845 3427.
E-mail address: bora.baysal@roswellpark.org.

0005-2728/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbabio.2012.12.005

The parent-of-origin specific transmission of tumor risk by *SDHD* and *SDHAF2* mutations is unusual for classical tumor suppressor genes and suggests functional differences between maternal and paternal alleles consistent with genomic imprinting. Genomic imprinting causes unequal expression of maternal and paternal alleles conferred by allele-specific epigenetic differences including DNA methylation or histone modifications [17]. However, for a long time, the molecular marks of genomic imprinting including differential methylation and monoallelic expression could not be identified at chromosome 11q23 and chromosome band 11q13, where *SDHD* and *SDHAF2* were located, respectively. The *SDHD* gene shows bi-allelic expression in a number of non-paraganglionic tissues [1]. The orthologous regions in mice containing the *Sdhd* and *Sdhaf2* genes on chromosome 9 show no evidence of imprinting [18], even though many imprinted loci are conserved between mice and human. In addition, paraganglioma tumors caused by germ line *SDHD* mutations demonstrate somatic loss of heterozygosity (LOH) targeting the unmutated maternal gene copy [19], suggesting that the maternal allele is expressed in paraganglionic tissues at least at low levels. Finally, as described below, paraganglioma development is recently suggested after maternal transmission of *SDHD* mutations in two isolated cases. These observations led to speculations that genomic imprinting might not be the mechanism responsible for the parent of origin effects.

It has been proposed that a distinct maternally expressed imprinted gene, presumably located within the imprinted gene clusters on the short arm of chromosome 11, must be lost by somatic whole chromosome deletions before PGL tumor development [20]. According to this model, when an *SDHD* mutation is inherited on the paternal allele, loss of entire maternal chromosome 11 eliminates both the normal non-imprinted maternal copy of *SDHD* and the putative maternally expressed distant imprinted gene. In contrast, when the *SDHD* mutation is inherited on the maternal allele, tumor development requires two more somatic hits: one hit to remove the normal paternal copy of *SDHD* and another hit to remove the maternal copy of the distant imprinted gene. Because somatic removal of distinct chromosome 11 segments from both maternal and paternal chromosomes is probabilistically unlikely, tumor development rarely occurs after the maternal transmission of an *SDHD* mutation.

In summary, this model assumes that PGL tumor development follows an unusual three hit process whereby both alleles of *SDHD* and maternal copy of a putative unlinked imprinted gene on chromosome 11 must be lost before tumor development. This model not only assumes a hypothetical unlinked maternally imprinted gene essential for paraganglioma tumor suppression, but also fails to explain why PGL tumors develop so frequently after transmission of a single mutation in the *SDHB* or *SDHC* genes, both located on chromosome 1. Because a requirement for the third hit targeting the putative imprinted gene on chromosome 11 should also make mutations in *SDHB* or *SDHC* virtually non-penetrant. In contrast, abundant data show that penetrance of *SDHB* and *SDHC* mutations are not low [2,21]. Therefore, the model incorporating somatic deletion of a third unlinked imprinted locus appears inadequate to explain the higher penetrance of SDH gene mutations in PGL.

Recently, paraganglioma development upon maternal transmission of *SDHD* mutations is observed in two cases from two families suggesting violation of the parent of origin effect observed in hundreds of *SDHD* families. In the first family, an 11 year old boy who inherited *SDHD* W42X mutation from his mother developed jugulotympanic paraganglioma [22]. The diagnosis of paraganglioma was suspected by angiography but could not be confirmed by histopathology. Remarkably, the tumor regressed after embolization and no other tumor was seen in the follow up exam performed 15 years later. In the second family, a histologically confirmed adrenal pheochromocytoma, the most common location for sporadic pheochromocytomas, developed in a 26 year old woman who inherited *SDHD* P81L mutation from her mother [23]. The tumor showed somatic loss of heterozygosity involving the paternal *SDHD* allele as well as maternal loss of markers at chromosome band 11p15. No other paraganglioma tumor was reported in the index case. It is notable that the expressivity of maternally transmitted *SDHD* mutations in both cases appears rather weak compared to that of the paternally-transmitted mutations in general. In the first index case, the jugulotympanic paraganglioma spontaneously regressed; in the second index case, a single adrenal pheochromocytoma is detected. In contrast, paternal transmission of *SDHD* mutations often causes highly penetrant paragangliomas that continues to grow slowly and that commonly develop in multiple locations in head/neck or extra-adrenal locations. Thus, even if the maternal transmission of *SDHD* mutations rarely causes PGL/PHEO, the resulting phenotype appears much milder compared to the phenotype after paternal transmission. Thus, as far as the penetrance and expressivity of the *SDHD* mutations is concerned, overall genetic data strongly suggest that the maternal and paternal copies of *SDHD* are functionally unequal, consistent with genomic imprinting.

3. Molecular evidence of imprinting at the SDHD locus

The observations described above, including possible rare cases of single tumor development after maternal transmission of risk mutations and the loss of heterozygosity targeting the maternal allele in PGL1 tumors, do not necessarily exclude a model based on quantitative tissue specific imprinting to explain the strong parent-of origin effects observed in the inheritance of *SDHD* and *SDHAF2* mutations. It should be noted that dosage of tumor suppressor genes strongly correlates with their tumor suppressing capability. Classical tumor suppressor genes often follow an autosomal dominant mode of transmission consistent with haploinsufficiency which triggers abnormal cell divisions and leads to tumor development following somatic loss of the normal unmutated allele. Accordingly, *Pten*-mediated tumor suppression appears to be highly dosage-sensitive in mouse in that as little as a 20% difference in gene expression may alter tumor suppressing capability of the *Pten* gene [24]. Tissue specific imprinting is also common occurrence. A recent analysis suggests that 28% of imprinted genes in mice may be imprinted only in one specific tissue, most commonly in placenta and brain [25]. Thus, a quantitative imprinting model with overexpression of the *SDHD* paternal allele relative to the maternal allele in paraganglionic tissues can explain the paternal transmission of tumor risk and the advantage conferred by LOH involving the maternal allele in the PGL1 tumors. Quantitative imprinting model has been also recently proposed by Muller [26] who argued that "reduced" expression of the maternal *SDHD* allele relative to the paternal allele can explain the imprinted tumor transmission because only a paternally transmitted mutation could deplete the gene product enough to trigger the hypoxic stimulation and tumor formation.

In support of the imprinting model, we recently identified a tissue-specific differentially methylated CpG island (CGI) that serves as an alternative promoter for a large intergenic non-coding RNA (linc RNA), located 200 kb downstream (telomeric) of the *SDHD* gene [27]. The linc RNA, which we referred as *UPGL*, marks a boundary between a gene-rich domain containing the *SDHD* gene and an approximately 800 kb long gene-desert. The methylation primarily occurred in adrenal tissues and involved two successive *Hpa*II restriction enzyme sites. The *UPGL* alternative promoter has two CGIs, each measuring approximately 300 bps, separated by a truncated LINE repeat. CGI#1 contains a strong CTCF/cohesin binding site. Whereas the more telomeric CGI#2 contains two differentially methylated *Hpa*II sites located 350 bp from the CTCF/cohesion binding site. Using rare heterozygous fetal specimens, we demonstrated unequal allelic methylation in fetal adrenal medulla and brain. Maternal hypermehylation is established in one case where maternal decidual tissue was available. Analysis of the alternative promoter methylation in paraganglioma tumors showed that non-*SDHD* tumors had more methylation than *SDHD* tumors in these two *Hpa*II sites suggesting that the maternal allelic loss that occurs in the *SDHD* tumors eliminates the hypermethylated maternal allele. Finally, mono-allelic expression of *UPGL* is demonstrated in adrenal gland and heart in one

fetal tissue. Altogether, these results provide molecular evidence of genomic imprinting at a CpG island distant from the *SDHD* gene.

Molecular evidence of imprinting at a gene-desert boundary flanking the *SDHD* locus is not limited to differential methylation and mono-allelic expression. We also noted remarkable genomic organizational similarities between the well-studied *IGF2-H19* imprinted genes and the *SDHD-UPGL* genes. In both regions, the upstream genes, *IGF2* and *SDHD*, are protein-encoding, paternally expressed and located at a significant distance from the downstream non-coding RNA genes *H19* and *UPGL*, respectively. It is thought that imprinted co-regulation of *IGF2* and *H19* genes involves competition for a common enhancer located downstream of both genes [28,29]. Enhancer competition is regulated by a chromatin boundary formed by CTCF and cohesin proteins [30] that bind to unmethylated maternal allele of a CpG island located upstream of the *H19* gene. This boundary prevents accessibility of the enhancer to *IGF2* promoter and favors expression of H19 gene in the maternal allele. Whereas methylation of the CpG island in the paternal allele blocks binding of CTCF and cohesin and allows the enhancer-*IGF2* promoter interaction, favoring paternal *IGF2* expression. Thus, a differentially-methylated CpG island serves as an imprint control region in the *IGF2*/*H19* locus by differentially binding CTCF/Cohesin proteins.

Remarkably, we also identified a strong CTCF binding site within the alternative promoter of the *UPGL* gene. However, in contrast to the *IGF2*/*H19* region the CTCF binding site within the alternative promoter was not methylated. The two differentially methylated *Hpa*II sites are located approximately 350 base pair telomeric to the core CTCF binding site. As expected, we found strong CTCF binding in both the methylated adrenal tissues and in unmethylated lung tissue. Surprisingly, strong cohesin binding occurred in the methylated adrenal gland but not in the unmethylated lung tissue. This finding suggests that cohesin engagement to CTCF may occur when the *Hpa*II sites are methylated, possibly in competition with a transcription factor binding to the *Hpa*II sites. Occupancy of unmethylated *Hpa*II sites by transcription factors may competitively block cohesin binding on the paternal allele. In contrast, blockage of transcription factor binding to methylated *Hpa*II sites (maternal allele) may allow cohesin engagement to CTCF. It is conceivable that chromatin architectural changes associated with allele-specific cohesin binding may result in differential long-range accessibility of a downstream enhancer to the *SDHD* promoter (Fig. 1). The model predicts that when the methylated *Hpa*II sites allows cohesin binding on the maternal allele, *SDHD* gene expression is low as a consequence of blocked enhancer–promoter interaction. In contrast, unmethylated *Hpa*II sites on the paternal allele blocks cohesin binding which in turn allows enhancer–promoter interaction resulting in increased *SDHD* gene expression.

It is notable that neither *UPGL* nor its differentially-methylated alternative promoter could be identified in the mouse orthologous region on chromosome 9, suggesting that this imprinted locus was absent in the common ancestor. Future work is needed to confirm the molecular marks of imprinting identified in this study and to test predictions of the long-range imprinted regulation model including presence of a *SDHD* enhancer downstream of *UPGL*. Whether the *UPGL* locus may also be involved in long-range imprinting regulation of the *SDHAF2* gene, which is located approximately 51 megabases upstream (centromeric) to *SDHD* on the long arm of chromosome 11 represents another line of future experimental inquiry.

4. Other regulatory mechanisms involving SDH subunits

In addition to the imprinted regulation of *SDHD* and *SDHAF2* genes, other SDH subunits may also be regulated by distinct genetic and post-translational mechanisms.

5. SDHA

The *SDHA* gene appears distinct from *SDHB*, *SDHC* and *SDHD* in that *SDHA* mutations have yet to be described in extended paraganglioma families. This finding suggests that penetrance of *SDHA* mutations may be low. Tissue culture experiments show that downregulation of *SDHB*, *SDHC* and *SDHD*, but not *SDHA*, by siRNA and drugs leads to increased ROS levels and hypoxia-inducible factor alpha (HIF-alpha) stabilization [31]. These findings suggest that *SDHA* might be expressed at much higher levels than the other subunit genes and that heterozygous mutations or downregulation by siRNA could not reduce protein levels enough to trigger ROS formation. Thus differential gene expression might be one mechanism of regulating SDH subunit activity.

A mouse knockout model of NAD(+)-dependent deacetylase, SIRT3, shows that reversible deacetylation of the SdhA gene product results in increased mitochondrial complex II activity [32]. When NAD(+) levels are high, SIRT3 may increase complex II activity to increase oxidative phosphorylation. *SDHA* protein product activity may also be regulated by phosphorylation through the activity of Fgr tyrosine kinase [33]. Recently, it has been suggested that *SDHA* protein product is also phosphorylated by c-Src protein kinase which may regulate cell viability and ROS production [34]. Perhaps, an interplay between phosphorylation and acetylation regulates complex II activity for cellular metabolic demands.

In addition to the post-translational regulation of *SDHA* protein product, distinct *SDHA* alleles are maintained at high concentrations in population. Sequence analysis of SDH structural subunits reveals an increased rate of *SDHA* polymorphisms, including two common missense variants Y629F and V657I, consistent with long-term balancing selection [35]. Balancing selection generally occurs when the heterozygote individuals have a survival advantage compared to homozygous individuals. Genetic signature of balancing selection in *SDHA* was present in humans but not in chimpanzees, suggesting that the selection occurred after the split of these species from their common ancestor. Selecting agents and functional consequences of the variants maintained at high frequencies are currently unclear.

6. SDHB

Analysis of *SDHB* transcripts derived from peripheral blood mononuclear cells has uncovered a targeted C-to-U mutation converting an arginine residue to a stop codon [36]. The mutation primarily occurs in monocytes. This observation suggests that *SDHB* mRNA is targeted by an unknown cytidine deaminase to decrease the gene dosage in certain blood cells. The biological significance and the underlying mechanism of this finding remain to be established.

7. Subunit composition change in lower organisms

While SDH is regulated by epigenetic mechanisms in human, changes in subunit composition plays an important role in oxygen dependent metabolism in lower organisms. Mitochondrial complex II has distinct enzymatic characteristics in different stages of the parasite *Ascaris Suum* (*A. Suum*). While larvae living in high oxygen concentrations use SDH, adult parasite living in low oxygen concentrations of intestine uses fumarate reductase (FRD) (reviewed in [37]). FRD uses fumarate as the final electron acceptor to produce succinate under anaerobic conditions. SDH in larvae and FRD in adult *A. Suum* have different *Sdha* and *Sdhd* protein products, whereas *Sdhb* protein product appears identical. Bacteria also have distinct FRD and SDH enzymes employed depending on the availability of oxygen. *Escherichia coli* FRD and SDH enzymes share no common subunits. These observations suggest that hypoxic environments are associated with a programmed switch in mitochondrial complex II enzyme activity from SDH to FRD in certain organisms.

8. Conclusions

Epigenetic regulation of mitochondrial complex II involves diverse mechanisms, including maternal imprinting of *SDHD* and *SDHAF2* genes, RNA editing of *SDHB* gene and common polymorphisms of the

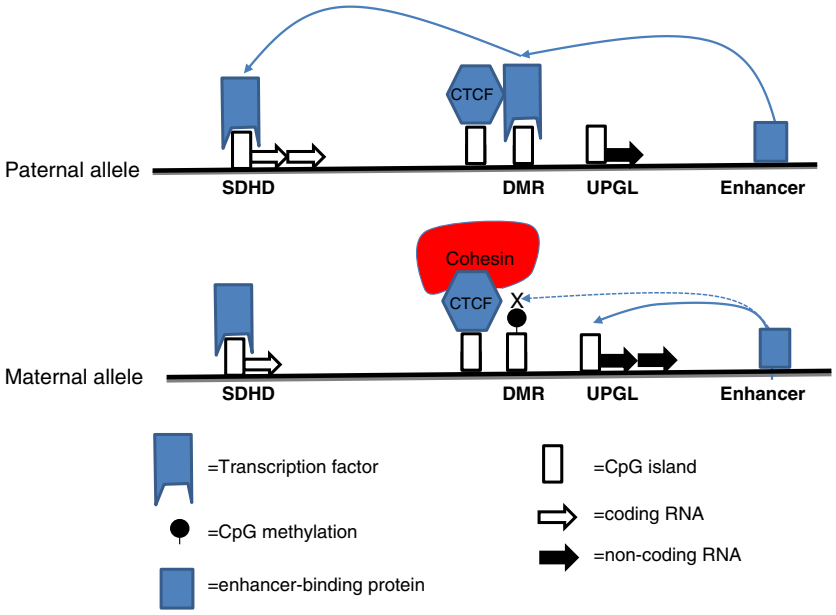

Fig. 1. A model for long-range epigenetic regulation of SDHD by genomic imprinting. A *cis*-acting element such as an enhancer may gain access to the *SDHD* promoter on the paternal allele, because cohesin engagement to CTCF may be competitively inhibited by a transcription factor bound to unmethylated alternative UPGL promoter. This long-range interaction may be blocked on the maternal allele where the alternative UPGL promoter is methylated, making the enhancer element instead available to the UPGL promoter.

SDHA gene, maintained by balancing selection. Because each structural and regulatory subunit is required for the function of complex II, epigenetic suppression of a single subunit is likely sufficient to downregulate the SDH enzymatic activity. Imprinted transmission pattern of *SDHD* and *SDHAF2* mutations was the first recognized evidence for epigenetic regulation of complex II. Studies in paraganglioma tumors demonstrate that complete inactivation of complex II by individual subunit mutations activates hypoxia inducible pathways. Thus, partial inactivation of complex II by distinct epigenetic mechanisms may act in synergy with environmental hypoxia to facilitate adaptation to low oxygen conditions.

Specifically, studies linking SDH regulation to hypoxia adaptation include (a) dynamic regulation of complex II enzymatic activities between FRD and SDH depending on oxygen availability in lower organisms [37]; (b) recapitulation of a chronic hypoxic phenotype of high altitudes (i.e., carotid body paragangliomas) by SDH mutations [1]; and (c) constitutive upregulation of hypoxia-inducible pathways in PGL tumors [38,39]. These findings collectively suggest that epigenetic downregulation of mitochondrial complex II in human may provide an advantage for early detection and/or adaptation to hypoxia in certain tissues. The occurrence of tissue-specific imprinting of *SDHD* in paraganglia, the most hypoxia sensitive tissue in the body, supports this conclusion. Despite these observations, role of mitochondrial complex II in oxygen sensing and signaling pathways remains poorly understood, although both succinate [40] and ROS [31] were implicated as downstream messengers that activate hypoxia-inducible pathways. Future research on epigenetic regulation of complex II subunits may help us better understand how this central metabolic enzyme integrates oxygen availability to diverse cellular processes.

References

[1] B.E. Baysal, R.E. Ferrell, J.E. Willett-Brozick, E.C. Lawrence, D. Myssiorek, A. Bosch, A. van der Mey, P.E. Taschner, W.S. Rubinstein, E.N. Myers, C.W. Richard III, C.J. Cornelisse, P. Devilee, B. Devlin, Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma, Science 287 (2000) 848–851.
[2] S. Niemann, U. Muller, Mutations in SDHC cause autosomal dominant paraganglioma, type 3, Nat. Genet. 26 (2000) 268–270.
[3] D. Astuti, F. Latif, A. Dallol, P.L. Dahia, F. Douglas, E. George, F. Skoldberg, E.S. Husebye, C. Eng, E.R. Maher, Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma, Am. J. Hum. Genet. 69 (2001) 49–54.
[4] H.X. Hao, O. Khalimonchuk, M. Schraders, N. Dephoure, J.P. Bayley, H. Kunst, P. Devilee, C.W. Cremers, J.D. Schiffman, B.G. Bentz, S.P. Gygi, D.R. Winge, H. Kremer, J. Rutter, SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma, Science 325 (2009) 1139–1142.
[5] G. Cecchini, Function and structure of complex II of the respiratory chain, Annu. Rev. Biochem. 72 (2003) 77–109.
[6] N. Burnichon, J.J. Briere, R. Libe, L. Vescovo, J. Riviere, F. Tissier, E. Jouanno, X. Jeunemaitre, P. Benit, A. Tzagoloff, P. Rustin, J. Bertherat, J. Favier, A.P. Gimenez-Roqueplo, SDHA is a tumor suppressor gene causing paraganglioma, Hum. Mol. Genet. 19 (2010) 3011–3020.
[7] E. Korpershoek, J. Favier, J. Gaal, N. Burnichon, B. van Gessel, L. Oudijk, C. Badoual, N. Gadessaud, A. Venisse, J.P. Bayley, M.F. van Dooren, W.W. de Herder, F. Tissier, P.F. Plouin, F.H. van Nederveen, W.N. Dinjens, A.P. Gimenez-Roqueplo, R.R. de Krijger, SDHA immunohistochemistry detects germline SDHA gene mutations in apparently sporadic paragangliomas and pheochromocytomas, J. Clin. Endocrinol. Metab. 96 (2011) E1472–6.
[8] B.E. Baysal, Hereditary paraganglioma targets diverse paraganglia, J. Med. Genet. 39 (2002) 617–622.
[9] H.P. Neumann, B. Bausch, S.R. McWhinney, B.U. Bender, O. Gimm, G. Franke, J. Schipper, J. Klisch, C. Altehoefer, K. Zerres, A. Januszewicz, C. Eng, W.M. Smith, R. Munk, T. Manz, S. Glaesker, T.W. Apel, M. Treier, M. Reineke, M.K. Walz, C. Hoang-Vu, M. Brauckhoff, A. Klein-Franke, P. Klose, H. Schmidt, M. Maier-Woelfle, M. Peczkowska, C. Szmigielski, C. Eng, Freiburg–Warsaw–Columbus Pheochromocytoma Study Group, Germ-line mutations in nonsyndromic pheochromocytoma, N. Engl. J. Med. 346 (2002) 1459–1466.
[10] H.J. Timmers, A.P. Gimenez-Roqueplo, M. Mannelli, K. Pacak, Clinical aspects of SDHx-related pheochromocytoma and paraganglioma, Endocr. Relat. Cancer 16 (2009) 391–400.
[11] A.G. van der Mey, P.D. Maaswinkel-Mooy, C.J. Cornelisse, P.H. Schmidt, J.J. van de Kamp, Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory, Lancet 2 (1989) 1291–1294.
[12] P. Heutink, A.G. van der Mey, L.A. Sandkuijl, A.P. van Gils, A. Bardoel, G.J. Breedveld, M. van Vliet, G.J. van Ommen, C.J. Cornelisse, B.A. Oostra, A gene subject to genomic imprinting and responsible for hereditary paragangliomas maps to chromosome 11q23-qter, Hum. Mol. Genet. 1 (1992) 7–10.
[13] B.E. Baysal, J.E. Farr, W.S. Rubinstein, R.A. Galus, K.A. Johnson, C.E. Aston, E.N. Myers, J.T. Johnson, R. Carrau, S.J. Kirkpatrick, D. Myssiorek, D. Singh, S. Saha, S.M. Gollin, G.A. Evans, M.R. James, C.W. Richard III, Fine mapping of an imprinted gene for familial nonchromaffin paragangliomas, on chromosome 11q23, Am. J. Hum. Genet. 60 (1997) 121–132.
[14] J. Milunsky, A.L. DeStefano, X.L. Huang, C.T. Baldwin, V.V. Michels, G. Jako, A. Milunsky, Familial paragangliomas: linkage to chromosome 11q23 and clinical implications, Am. J. Med. Genet. 72 (1997) 66–70.
[15] E.C. Mariman, S.E. van Beersum, C.W. Cremers, P.M. Struycken, H.H. Ropers, Fine mapping of a putatively imprinted gene for familial non-chromaffin paragangliomas to chromosome 11q13.1: evidence for genetic heterogeneity, Hum. Genet. 95 (1995) 56–62.
[16] H.P. Kunst, M.H. Rutten, J.P. de Monnink, L.H. Hoefsloot, H.J. Timmers, H.A. Marres, J.C. Jansen, H. Kremer, J.P. Bayley, C.W. Cremers, SDHAF2 (PGL2-SDH5) and hereditary head and neck paraganglioma, Clin. Cancer Res. 17 (2011) 247–254.

[17] L.K. Abramowitz, M.S. Bartolomei, Genomic imprinting: recognition and marking of imprinted loci, Curr. Opin. Genet. Dev. 22 (2012) 72–78.
[18] I.M. Morison, J.P. Ramsay, H.G. Spencer, A census of mammalian imprinting, Trends Genet. 21 (2005) 457–465.
[19] E.M. van Schothorst, M. Beekman, P. Torremans, N.J. Kuipers-Dijkshoorn, H.W. Wessels, A.F. Bardoel, A.G. van der Mey, M.J. van der Vijver, G.J. van Ommen, P. Devilee, C.J. Cornelisse, Paragangliomas of the head and neck region show complete loss of heterozygosity at 11q22–q23 in chief cells and the flow-sorted DNA aneuploid fraction, Hum. Pathol. 29 (1998) 1045–1049.
[20] E.F. Hensen, E.S. Jordanova, I.J. van Minderhout, P.C. Hogendoorn, P.E. Taschner, A.G. van der Mey, P. Devilee, C.J. Cornelisse, Somatic loss of maternal chromosome 11 causes parent-of-origin-dependent inheritance in SDHD-linked paraganglioma and phaeochromocytoma families, Oncogene 23 (2004) 4076–4083.
[21] H.P. Neumann, C. Pawlu, M. Peczkowska, B. Bausch, S.R. McWhinney, M. Muresan, M. Buchta, G. Franke, J. Klisch, T.A. Bley, S. Hoegerle, C.C. Boedeker, G. Opocher, J. Schipper, A. Januszewicz, C. Eng, European–American Paraganglioma Study Group, Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations, JAMA 292 (2004) 943–951.
[22] P. Pigny, A. Vincent, C. Cardot Bauters, M. Bertrand, V.T. de Montpreville, M. Crepin, N. Porchet, P. Caron, Paraganglioma after maternal transmission of a succinate dehydrogenase gene mutation, J. Clin. Endocrinol. Metab. 93 (2008) 1609–1615.
[23] P.M. Yeap, E.S. Tobias, E. Mavraki, A. Fletcher, N. Bradshaw, E.M. Freel, A. Cooke, V.A. Murday, H.R. Davidson, C.G. Perry, R.S. Lindsay, Molecular analysis of pheochromocytoma after maternal transmission of SDHD mutation elucidates mechanism of parent-of-origin effect, J. Clin. Endocrinol. Metab. 96 (2011) E2009–13.
[24] A. Alimonti, A. Carracedo, J.G. Clohessy, L.C. Trotman, C. Nardella, A. Egia, L. Salmena, K. Sampieri, W.J. Haveman, E. Brogi, A.L. Richardson, J. Zhang, P.P. Pandolfi, Subtle variations in Pten dose determine cancer susceptibility, Nat. Genet. 42 (2010) 454–458.
[25] A.R. Prickett, R.J. Oakey, A survey of tissue-specific genomic imprinting in mammals, Mol. Genet. Genomics 287 (2012) 621–630.
[26] U. Muller, Pathological mechanisms and parent-of-origin effects in hereditary paraganglioma/pheochromocytoma (PGL/PCC), Neurogenetics 12 (2011) 175–181.
[27] B.E. Baysal, S.E. McKay, Y.J. Kim, Z. Zhang, L. Alila, J.E. Willett-Brozick, K. Pacak, T.H. Kim, G.S. Shadel, Genomic imprinting at a boundary element flanking the SDHD locus, Hum. Mol. Genet. 20 (2011) 4452–4461.
[28] A.T. Hark, C.J. Schoenherr, D.J. Katz, R.S. Ingram, J.M. Levorse, S.M. Tilghman, CTCF mediates methylation-sensitive enhancer-blocking activity at the H19/Igf2 locus, Nature 405 (2000) 486–489.
[29] A.C. Bell, G. Felsenfeld, Methylation of a CTCF-dependent boundary controls imprinted expression of the Igf2 gene, Nature 405 (2000) 482–485.
[30] K.S. Wendt, K. Yoshida, T. Itoh, M. Bando, B. Koch, E. Schirghuber, S. Tsutsumi, G. Nagae, K. Ishihara, T. Mishiro, K. Yahata, F. Imamoto, H. Aburatani, M. Nakao, N. Imamoto, K. Maeshima, K. Shirahige, J.M. Peters, Cohesin mediates transcriptional insulation by CCCTC-binding factor, Nature 451 (2008) 796–801.
[31] R.D. Guzy, B. Sharma, E. Bell, N.S. Chandel, P.T. Schumacker, Loss of the SdhB, but Not the SdhA, subunit of complex II triggers reactive oxygen species-dependent hypoxia-inducible factor activation and tumorigenesis, Mol. Cell. Biol. 28 (2008) 718–731.
[32] H. Cimen, M.J. Han, Y. Yang, Q. Tong, H. Koc, E.C. Koc, Regulation of succinate dehydrogenase activity by SIRT3 in mammalian mitochondria, Biochemistry 49 (2010) 304–311.
[33] M. Salvi, N.A. Morrice, A.M. Brunati, A. Toninello, Identification of the flavoprotein of succinate dehydrogenase and aconitase as in vitro mitochondrial substrates of Fgr tyrosine kinase, FEBS Lett. 581 (2007) 5579–5585.
[34] M. Ogura, J. Yamaki, M.K. Homma, Y. Homma, Mitochondrial c-Src regulates cell survival through phosphorylation of respiratory chain components, Biochem. J. 447 (2012) 281–289.
[35] B.E. Baysal, E.C. Lawrence, R.E. Ferrell, Sequence variation in human succinate dehydrogenase genes: evidence for long-term balancing selection on SDHA, BMC Biol. 5 (2007) 12.
[36] B.E. Baysal, A recurrent stop-codon mutation in succinate dehydrogenase subunit B gene in normal peripheral blood and childhood T-cell acute leukemia, PLoS One 2 (2007) e436.
[37] K. Kita, H. Hirawake, H. Miyadera, H. Amino, S. Takeo, Role of complex II in anaerobic respiration of the parasite mitochondria from *Ascaris suum* and *Plasmodium falciparum*, Biochim. Biophys. Acta 1553 (2002) 123–139.
[38] P.L. Dahia, K.N. Ross, M.E. Wright, C.Y. Hayashida, S. Santagata, M. Barontini, A.L. Kung, G. Sanso, J.F. Powers, A.S. Tischler, R. Hodin, S. Heitritter, F. Moore, R. Dluhy, J.A. Sosa, I.T. Ocal, D.E. Benn, D.J. Marsh, B.G. Robinson, K. Schneider, J. Garber, S.M. Arum, M. Korbonits, A. Grossman, P. Pigny, S.P. Toledo, V. Nose, C. Li, C.D. Stiles, A HIF1alpha regulatory loop links hypoxia and mitochondrial signals in pheochromocytomas, PLoS Genet. 1 (2005) 72–80.
[39] E. Lopez-Jimenez, G. Gomez-Lopez, L.J. Leandro-Garcia, I. Munoz, F. Schiavi, C. Montero-Conde, A.A. de Cubas, R. Ramires, I. Landa, S. Leskela, A. Maliszewska, L. Inglada-Perez, L. de la Vega, C. Rodriguez-Antona, R. Leton, C. Bernal, J.M. de Campos, C. Diez-Tascon, M.F. Fraga, C. Boullosa, D.G. Pisano, G. Opocher, M. Robledo, A. Cascon, Research resource: transcriptional profiling reveals different pseudohypoxic signatures in SDHB and VHL-related pheochromocytomas, Mol. Endocrinol. 24 (2010) 2382–2391.
[40] M.A. Selak, S.M. Armour, E.D. MacKenzie, H. Boulahbel, D.G. Watson, K.D. Mansfield, Y. Pan, M.C. Simon, C.B. Thompson, E. Gottlieb, Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase, Cancer Cell 7 (2005) 77–85.