Current views on cell metabolism in *SDHx*-related pheochromocytoma and paraganglioma

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Abstract

Warburg's metabolic hypothesis is based on the assumption that a cancer cell's respiration must be under attack, leading to its damage, in order to obtain increased glycolysis. Although this may not apply to all cancers, there is some evidence proving that primarily abnormally functioning mitochondrial complexes are indeed related to cancer development. Thus, mutations in complex II (succinate dehydrogenase (SDH)) lead to the formation of pheochromocytoma (PHEO)/paraganglioma (PGL). Mutations in one of the *SDH* genes (*SDHx* mutations) lead to succinate accumulation associated with very low fumarate levels, increased glutaminolysis, the generation of reactive oxygen species, and pseudohypoxia. This results in significant changes in signaling pathways (many of them dependent on the stabilization of hypoxia-inducible factor), including oxidative phosphorylation, glycolysis, specific expression profiles, as well as genomic instability and increased mutability resulting in tumor development. Although there is currently no very effective therapy for *SDHx*-related metastatic PHEOs/PGLs, targeting their fundamental metabolic abnormalities may provide a unique opportunity for the development of novel and more effective forms of therapy for these tumors.

Key Words
- SDHx
- glycolysis
- Warburg effect
- reactive oxygen species
- succinate dehydrogenase
- pheochromocytoma
- paraganglioma
- renal cell carcinoma
- gastrointestinal stromal tumor
- hypoxia
- pseudohypoxia

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Introduction

In previous innovative work, Hanahan & Weinberg (2000) determined the unique hallmarks of cancer that together constitute a fundamental principle that provides a logical framework for understanding the remarkable diversity, yet nevertheless similarity, of various cancers. Six hallmarks of cancer, namely sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, promoting angiogenesis, and resisting cell death, are the driving forces that ultimately cause cancer cell development and spread, leading to patient death (Hanahan & Weinberg 2000). Recently, Hanahan & Weinberg (2011) have added two new emerging hallmarks: evading immune destruction and reprograming energy metabolism.

Additional scientific studies have also shown that altered energy metabolism is as widespread in cancer cells as many of the other cancer-associated traits that have been well accepted as the hallmarks of cancer

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(Levine & Puzio-Kuter 2010). This raises the question of whether deregulating cellular energy metabolism could be a core hallmark of cancer cells. In fact, redirection of energy metabolism is largely orchestrated by proteins that are involved in one way or another in programing the core hallmarks of cancer. When viewed in this way, abnormal oxidative phosphorylation (OXPHOS) is simply another phenotype that is caused by altered oncogenes or tumor suppressor genes (Levine & Puzio-Kuter 2010). Multiple lines of evidence indicate that the process of tumorigenesis is often associated with altered metabolism. In 1926, Otto Warburg reported that cancer cells produce most of their ATP via 'aerobic glycolysis' (Warburg *et al*. 1926). A significant glycolytic production of ATP despite aerobic conditions, referred to as the Warburg effect, was found to be the characteristic of most cancer cells (Warburg 1956). Warburg reasoned that respiration must be damaged in cancers because high levels of O_2 are unable to suppress the production of lactic acid by cancer cells (known as the Pasteur effect). However, new studies have demonstrated that tumor mitochondria are fairly functional with regards to respiration and ATP synthesis, exhibiting almost normal respiratory control ratios and capabilities for the oxidation of respiratory substrates (Eakin *et al*. 1972, Bensinger & Christofk 2012, Krejci 2012, Nakajima & Van Houten 2013).

Although mitochondria are fairly functional in the majority of cancers, some cancers were found with mutations in the genes linked to paramout mitochondrial processes, the Krebs cycle (tricarboxylic acid cycle (TCA); Linehan & Rouault 2013, Zhang *et al*. 2013) and OXPHOS. Mitochondrial complex II, also known as succinate dehydrogenase (SDH), is one such protein involved in both TCA and OXPHOS. This membrane complex catalyzes the oxidation of succinate to fumarate in TCA and serves as an electron donor to complex III via CoQ (Eng *et al*. 2003, Gottlieb & Tomlinson 2005). Succinate oxidation results in the reduction of ubiquinone (CoQ) to ubiquinol at the mitochondrial inner membrane as one part of the respiration electron transfer chain (Sun *et al*. 2005*a*). SDH is composed of four subunits (SDHA–D), all encoded by nuclear genes (Baysal 2003, 2008, Yankovskaya *et al*. 2003, Sun *et al*. 2005*b*, Cascon *et al*. 2008). The large SDHA subunit is catalytic. The conversion of succinate to fumarate is accomplished by SDHA through the reduction of a flavin adenine dinucleotide, a molecule bound to its protein moiety. This reaction is measured as SDH activity. Electrons are then passed to three Fe–S centers bound to SDHB, which eventually transfers them to ubiquinone (coenzyme Q). The smaller subunits, SDHC and SDHD, bind ubiquinone and anchor the entire complex to the inner membrane of the mitochondria (Rustin *et al*. 2002).

Deleterious mutations in any of the *SDH* genes invariably result in decreased SDH activity or a significant reduction or complete absence of the protein (Rustin *et al*. 2002, van Nederveen *et al*. 2009, Gill *et al*. 2011, Korpershoek *et al*. 2011, Yang *et al*. 2012). Inherited defects in particular SDH subunits in humans are associated with variable clinical presentations ranging from early-onset devastating encephalomyopathy to tumor susceptibility or optic atrophy. Homozygous or compound heterozygous mutations in *SDHA* cause metabolic neurodegenerative disorders like congenital Leigh syndrome and late-onset optic atrophy, ataxia, and myopathy (Birch-Machin *et al*. 2000, Parfait *et al*. 2000, Horvath *et al*. 2006, Burnichon *et al*. 2010, Levitas *et al*. 2010). Recently, Alston *et al*. (2012) have presented the first patient with hypotonia and leukodystrophy due to a novel homozygous *SDHB* mutation. Heterozygous mutations in *SDHA–D* predispose to tumorigenesis (Fig. 1; Maher & Eng 2002, Astuti *et al*. 2003, 2004, Eng *et al*. 2003, Schiavi *et al*. 2005, Bayley *et al*. 2006, Benn *et al*. 2006, Cascon *et al*. 2008). The detailed molecular and cellular mechanisms linking these latter *SDH* mutations and tumorigenesis have not been fully elucidated. Thus, consistent with Knudson's two-hit hypothesis for tumorigenesis, a heterozygous germline mutation in an *SDH* gene is associated with a loss of the WT allele, or other silencing mechanisms (e.g. methylation) of the WT allele are present in a tumor (Baysal *et al*. 2000, Astuti *et al*. 2003, 2004, Baysal 2003, 2004, 2008, Eng *et al*. 2003, Gimenez-Roqueplo *et al*. 2003, Ni *et al*. 2008, 2012, Sandgren *et al*. 2010, Bardella *et al*. 2011, Killian *et al*. 2013, Letouze *et al*. 2013) as the starting point for tumor development. Moreover, the pathophysiology of distinct clinical phenotypes associated with abnormalities in SDH subunits remains to be determined (Timmers *et al*. 2009*a*). Detailed knowledge about *SDH* mutations is available in a database (LOVD, v.2.0 (Leiden Open Variation Database), http://www.lovd.nl/2.0; Bayley *et al*. 2005).

Although these findings led to a renewed interest in cancer metabolism, our knowledge on the specifics of tumor metabolism is still fragmented. Nevertheless, multiple lines of evidence indicate that the process of tumorigenesis is often associated with altered metabolism. In this review, we show and discuss how mutations in *SDH* subunits can lead to reprograming of cancer-related metabolism. Also, this paper reviews recent findings

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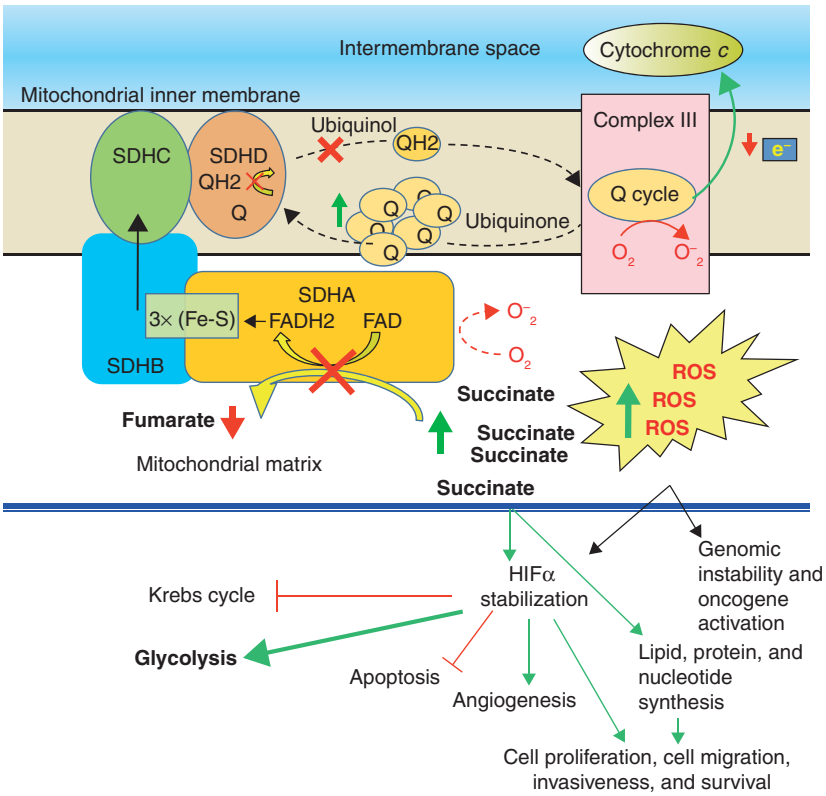

Figure 1

The succinate dehydrogenase complex (SDH), as a member of the tricarboxylic acid cycle (TCA), catalyzes the oxidation of succinate to fumarate. In this reaction, two hydrogen atoms are removed from succinate by FAD. These electrons from the reduced SDH–$FADH_2$ complex are then transferred to ubiquinol–ubiquinone (coenzyme Q), a soluble component of the electron transport system of complex II. In the Q cycle, the sequential oxidation and reduction of the lipophilic electron carrier, coenzyme Q, generates protons that are transferred to complex III, with the ultimate generation of ATP (complex V). Coenzyme Q, beside its function in the respiratory chain as an electron carrier mediating electron transfer between the various dehydrogenases and the cytochrome pathway, also works as a powerful antioxidant in biological membranes. Dysfunction of SDH inactivates the electron transport chain and the Krebs cycle. A lack or suboptimal level of SDH activity will not only cause decreased ATP production, but will also result in increased ROS with succinate accumulation. An increase in ROS, like the accumulation of succinate, leads to stabilization of HIFα. HIFα stabilization subsequently activates glycolysis, cell proliferation, cell migration, invasiveness, and angiogenesis and inhibits apoptosis. The overexpression of ROS triggers genomic instability, oncogene activation, and tumor suppressor inactivation. e^-, electron; FAD, flavin adenine dinucleotide; $FADH_2$, FAD hydroquinone; ROS, reactive oxygen species; Q, ubiquinone; QH2, ubiquinol; SDHA, B, C, and D, succinate dehydrogenase complex subunits A, B, C, and D.

related to key metabolites, transcription factors, and enzymes that play an important role in the regulation of cancer metabolism, and that blocking these metabolic pathways or restoring altered pathways can lead to new approaches in cancer treatment.

Pheochromocytoma and paraganglioma

Pheochromocytomas (PHEOs)/paragangliomas (PGLs) are rare neuroendocrine tumors that produce catecholamines (Lenders *et al*. 2005). PHEOs/PGLs arise from three distinct parts of the neural crest: the adrenal medulla (PHEOs) and the sympathetic and parasympathetic paraganglia (extradrenal PGLs) (Papaspyrou *et al*. 2012).

One-third or more of PHEO/PGL cases have a familial etiology (Neumann *et al*. 2002, Erlic *et al*. 2009, Gimenez-Roqueplo *et al*. 2012). This group is heterogeneous with diverse hereditary backgrounds due to germ line mutations in 16 susceptibility genes to date. Some of these include neurofibromatosis type 1 (*NF1*; Viskochil *et al*. 1990), the ret proto-oncogene (*RET*; Mulligan *et al*. 1993), the von Hippel–Lindau (*VHL*; Latif *et al*. 1993) tumor suppressor, the *SDH* subunits (*SDHA/B/C/D*; Baysal *et al*. 2000, Niemann & Muller 2000, Astuti *et al*. 2001, Burnichon *et al*. 2010), SDH complex assembly factor 2 (*SDHAF2*; Hao *et al*. 2009), transmembrane protein 127 (*TMEM127*; Qin *et al*. 2010, Yao *et al*. 2010, Jiang & Dahia 2011), the MAX protein (*MAX*; Comino-Mendez *et al*. 2011), kinesin

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family member 1B (*KIF1B*; Schlisio *et al*. 2008, Yeh *et al*. 2008), the 2-oxoglutarate (2OG)-dependent prolyl hydroxylase enzymes (*PHD2*, Ladroue *et al*. 2008, Eltzschig *et al*. 2009), isocitrate dehydrogenase 1 (*IDH1*; Gaal *et al*. 2010), and most recently hypoxia-inducible transcription factor 2α (*HIF2A*; Zhuang *et al*. 2012, Toledo *et al*. 2013), fumarate hydratase (*FH*; Castro-Vega *et al*. 2013), and H-RAS protein (*H-RAS*; Crona *et al*. 2013). Somatic mutations of these genes are also involved in PHEO/PGL tumors (Burnichon *et al*. 2012*a*, Weber *et al*. 2012, Crona *et al*. 2013, Dahia 2013). Hereditary and sporadic PHEOs/PGLs can be divided into two groups based on their transcription profile revealed by genome-wide expression microarray analysis (Lopez-Jimenez *et al*. 2010, Burnichon *et al*. 2011, Galan & Kann 2013, Vicha *et al*. 2013). The first group (cluster 1) includes tumors carrying *VHL* and *SDHx* (*SDHD*, *SDHB*, *SDHC*, *SDHA*, and *SDHAF2*) mutations and also accounts for about 30% of sporadic tumors (Dahia *et al*. 2005, Lopez-Jimenez *et al*. 2010, Burnichon *et al*. 2011). The second group (cluster 2) represents tumors carrying *NF1*, *RET*, and *KIF1Bβ* mutations, and also includes about 70% of sporadic tumors (Burnichon *et al*. 2011, Gimenez-Roqueplo *et al*. 2012, Shah *et al*. 2012, Galan & Kann 2013). The newly discovered *TMEM127* and *MAX* genes are most likely associated with cluster 2, and HIF2α with cluster 1 (Burnichon *et al*. 2011, 2012*b*, Lorenzo *et al*. 2012, Zhuang *et al*. 2012). However, a subset of *MAX*-related tumors may have impaired SDH activity, and metabolomics in these tumors could uncover new data that could be very useful clinically for their diagnosis (Rapizzi *et al*. 2012).

In cluster 1, *VHL/SDHx* mutations lead to impaired degradation and accumulation of HIF1/2α and display signatures of pseudohypoxia, angiogenesis, increased reactive oxygen species (ROS), and reduced oxidative response resulting in changes in cell metabolism (energy metabolism regulation). *VHL* and *SDH* subunit mutations distribute tumors to separate subclusters within cluster 1 (Eisenhofer *et al*. 2004, Dahia *et al*. 2005, Burnichon *et al*. 2009, Lopez-Jimenez *et al*. 2010). Cluster 2-related PHEOs/PGLs are linked together by the activation of kinase signaling pathways driven by oncogenes that are involved in kinase signaling, translation, initiation, protein synthesis, and genes involved in neural/neuroendocrine identity (Dahia *et al*. 2005, Powers *et al*. 2007, Yeh *et al*. 2008, Burnichon *et al*. 2011, Jiang & Dahia 2011, Shah *et al*. 2012). Cluster 1 is characterized by immature catecholamine phenotypic features of associated tumors (Eisenhofer *et al*. 2004). The immature phenotype involves reduced or absent expression of numerous catecholamine biosynthetic and secretory pathway components, mainly phenylethanolamine *N*-methyltransferase, the enzyme that converts norepinephrine to epinephrine (Eisenhofer *et al*. 2011*a*, 2012). Also, *SDH*-related tumors often produce dopamine. Thus, cluster 1 tumors can be distinguished from cluster 2 tumors by the absence of epinephrine production (Eisenhofer *et al*. 2004, 2011*a*,*b*, Burnichon *et al*. 2012*b*, Eisenhofer *et al*. 2012). Most recently, Imperiale *et al*. (2013) evaluated metabolic characteristics of PHEOs/PGLs tumors, using ^{1}H high-resolution magic angle spinning nuclear magnetic resonance (HRMAS-NMR) spectroscopy. *SDHx*-related tumors were characterized by an increase in succinate levels, significantly lower values of glutamate, and lower values of ATP/ADP/AMP in *SDHx*-related tumors compared with other subtypes. *VHL* tumors were found to have the highest values of glutathione (GSH) compared with other PHEOs/PGLs. This study showed that HRMAS-NMR spectroscopy is a future promising method for investigating the metabolomic profile of various PHEOs/PGLs.

SDH dysfunction and metabolic changes

Succinate accumulation

It is well documented that abnormal SDH function induces an accumulation of succinate (Selak *et al*. 2005, King *et al*. 2006, Hobert *et al*. 2012, Rao *et al*. 2013). Very recently, Lendvai *et al*. (2013) showed that tissue levels of succinate in PGLs due to *SDHB/D* mutations were several-fold higher. Their results showed that the mean fumarate concentration in *SDHB*-related PGLs is significantly lower than in the apparently sporadic PHEO/PGL group. Lendvai *et al*. (2013) also demonstrated a significantly increased succinate:fumarate ratio in *SDHB*-related PGLs and suggested that this ratio may be used as a new metabolic marker for the detection of *SDHB*-related PHEOs/PGLs. Thus, mass spectrometric-based measurements of succinate:fumarate ratios in PHEO/PGL tumor tissue may provide a novel method to identify patients to be tested for SDHB/C/D mutations. The measurements could also be useful for assessing metabolic factors responsible for variable clinical presentations of tumors resulting from mutations of different *SDHx* genes. Also, plasma organic acid analysis may provide an effective and inexpensive screening method to determine the presence of *SDHx* mutations in the near future (Hobert *et al*. 2012).

The accumulation of specific metabolites has been illustrated in different tumor models with inherited and acquired alterations of enzymes of the TCA cycle, such as

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fumarate in cases of *FH* gene mutations (Isaacs *et al*. 2005) and 2-hydroxyglutarate in mutations in one of the two *IDH* genes (*IDH1/2*) (Dang *et al*. 2009). These findings have important implications for our understanding of tumorigenesis because these metabolites convey oncogenic signals (oncometabolites; Kaelin & McKnight 2013).

Succinate that accumulates in the mitochondrial matrix due to SDH dysfunction leaks out into the cytosol, where it inhibits the activity of HIF1/2α PHDs (PHD1, 2, and 3, also known as EGLN2, 1, and 3 respectively) that hydroxylate two prolyl residues (Dann & Bruick 2005). PHDs are members of a large superfamily of α-ketoglutarate-dependent dioxygenases. PHD action normally requires oxygen and α-ketoglutarate as cosubstrates and ferrous iron and ascorbate as cofactors. (Hewitson *et al*. 2003, Kaelin & Ratcliffe 2008). Succinate competes with α-ketoglutarate in binding to the PHD enzyme. Therefore, increasing succinate levels offset the effect of PHD activity. A lack of SDH activity inhibits succinate–ubiquinone activity; thus, electrons that would normally transfer through the SDHB subunit to the ubiquinone pool are instead donated to molecular oxygen to give a superoxide anion with a subsequent increase in ROS production and oxidative stress. ROS exposure also inhibits the interaction of HIFα and PHDs, similar to the accumulation of succinate, but it is proposed that such an inhibition of this interaction by ROS may be more important for tumorigenesis (Yankovskaya *et al*. 2003, Guzy *et al*. 2008, Majmundar *et al*. 2010). The inhibition of the HIFα–PHD interaction leads to the stabilization of HIFα and activation of the HIF complex (Lee *et al*. 2005). HIFα regulates the transcription of a number of genes that are known to be involved in tumorigenesis and angiogenesis, extracellular matrix elements, and coordinated suppression of oxidoreductase enzymes, all processes that would be directly or indirectly regulated by the activation of HIF1α and/or HIF2α (Dahia *et al*. 2005, Selak *et al*. 2005, Mole *et al*. 2009, Favier & Gimenez-Roqueplo 2010, Semenza 2010, 2011, 2012, Keith *et al*. 2012). HIF1α and HIF2α regulate both shared and unique target genes and pathways. The common shared targets are vascular endothelial growth factor (VEGF), GLUT1, GLUT3, and hexokinase 2 (HK2). HIF1α exclusively stimulates the expression of several glycolytic enzymes, whereas the embryonic transcription factors Oct4, cyclin D1, platelet-derived growth factor, and erythropoietin are activated in a HIF2α-dependent manner (Fig. 2; Rankin *et al*. 2007, Patel & Simon 2008, Furlow *et al*. 2009, Florczyk *et al*. 2011, Koh *et al*. 2011, Franke *et al*. 2013, Singh *et al*. 2013). The differential effects of these two transcription factors in numerous cellular systems are now well established and reviewed, including their link to the pathogenesis of PHEO and PGL (Holmquist-Mengelbier *et al*. 2006, Koh *et al*. 2011, Branco-Price *et al*. 2012, Chiavarina *et al*. 2012, Keith *et al*. 2012, Semenza 2012, Jochmanova *et al*. 2013). Despite the fact that Pollard *et al*. (2005, 2006) found relatively more common HIF2α overexpression in *VHL* PHEOs and PGLs, whereas in *SDHx*-related tumors nuclear HIF1α staining was more prominent, Gimenez-Roqueplo *et al*. (2001, 2002) described overexpression of HIF2α and VEGF in patients with PHEOs and PGLs carrying *SDHB* and *SDHD* mutations compared with sporadic PHEOs and PGLs, and Favier *et al*. (2009) found overexpression of *HIF2α* mRNA in both *VHL* and *SDH*-related PHEO and PGL. Also, Eisenhofer *et al*. (2004) and Koh *et al*. (2011) support the leading role of HIF2α in the tumor development and progression in cluster 1 tumors as well as their unique noradrenergic phenotype (Jochmanova *et al*. 2013). The important role of HIF2α in various developmental issues is also supported by previous observations performed in fetal paraganglia and neuroblastoma (Tian *et al*. 1998, Favier *et al*. 1999, Nilsson *et al*. 2005, Jochmanova *et al*. 2013).

Similarly, the mechanism of PHD inhibition by succinate is likely to extend to other numbers of a large superfamily of α-ketoglutarate-dependent dioxygenases. One of them is the factor inhibiting HIF, which normally hydroxylates HIF1α on the asparagine 803 residue. This blocks its interaction with the coactivators histone acetyltransferase p300 (p300) and cAMP-response element-binding protein under normoxic conditions (Mahon *et al*. 2001, Lando *et al*. 2002) and thus inhibits the transactivation of HIF target genes (Khan *et al*. 2011, Cascon & Tennant 2012). Also, *SDHx* mutations inhibit the activity of the jumonji-domain (JmjC) histone demethylases (Cervera *et al*. 2009, Xiao *et al*. 2012). These enzymes use α-ketoglutarate to remove the methyl groups found on arginines and lysines of histones H3 and H4 (Agger *et al*. 2008). *SDHx* mutations decrease histone demethylase activity (specifically the JMJD3 demethylase) and lead to increased methylation of histone H3 (H3K27me3) (Cervera *et al*. 2009). Similarly, very recently Letouze *et al*. (2013) showed that increased tumor levels of succinate lead to DNA hypermethylation, a process causing global changes in gene expression as a critical tumorigenic mechanism. These modulations in the pseudohypoxic signature observed in *SDHx*-related tumors can distinguish the gene expression phenotypes observed in the two subgroups of tumors in cluster 1.

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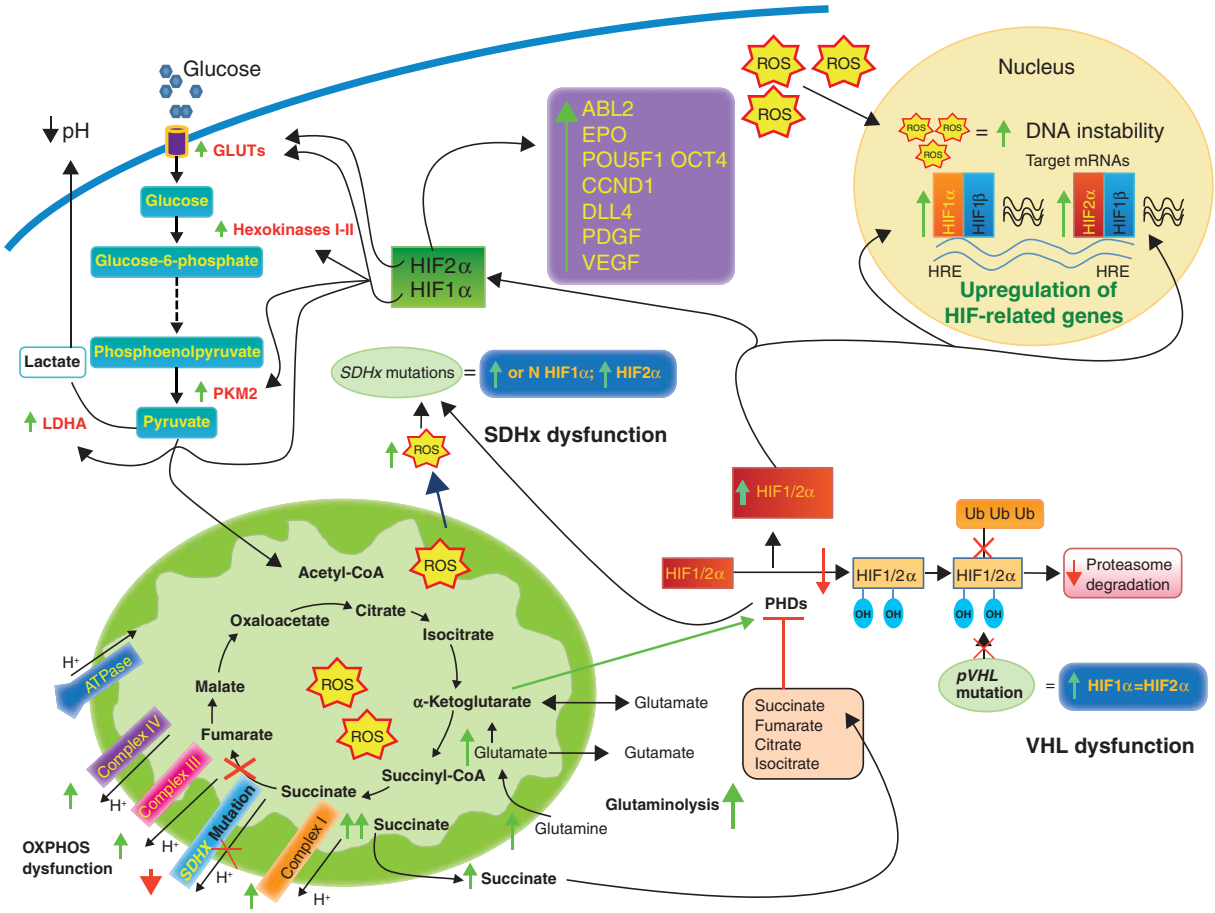

Figure 2

Different mechanisms have been proposed to explain the link between *SDHx* mutations and tumorigenesis. First, the loss of function of SDH causes an accumulation of succinate and the overproduction of ROS. Second, inactivation or dysfunction of SDH inhibits the activity of HIFα PHDs. Inhibition of PHDs results in an insufficient hydroxylation of HIF1/2α. The unhydroxylated HIF1/2α protein cannot be degraded by the proteasome, and HIF1/2α is stabilized. This stabilization can be overcome by α-ketoglutarate. *VHL* mutations result in similar inadequate HIF1/2α proteasome degradation and HIF1/2α stabilization. The stabilization of HIF1α rather than HIF2α increases glycolysis (due to overexpression of some glycolytic enzymes) and can regulate glutaminolysis. HIF2α stabilization is involved in the direct or indirect activation of a number of genes that are known to be involved in the inhibition of apoptosis, tumorigenesis, and angiogenesis. The stabilization of HIF1/2α leads to an upregulation of HIF-related genes due to binding to HREs and to an overexpression of hypoxia-related genes. Increased ROS accumulation results in oxidative DNA damage and genomic instability and inhibits PHDs, similarly to the accumulation of succinate. Increasing activity of complex I, III, and IV may be a compensatory reaction to a lack of, or decreased, complex II activity in *SDHx*-related tumors. ABL2, ABL2 protein tyrosine-protein kinase; CCDN1, cyclin D1; DLL4, delta-like protein 4; EPO, erythropoietin; GLUTs, glucose transporters; HIF, hypoxia-inducible factor; HREs, hypoxia-responsive elements; LDH-A, lactate dehydrogenase A; OXPHOS, oxidative phosphorylation; PDGF, platelet-derived growth factor; PHDs, prolyl hydroxylases; PKM2, pyruvate kinase muscle isozyme 2; POU5F1 OCT4, POU domain, class 5, tarnscription factor 1 isoform; pVHL, protein of the von Hippel–Lindau tumor suppressor gene; ROS, reactive oxygen species; SDH, succinate dehydrogenase; Ub, ubiquitin; VEGF, vascular endothelial growth factor.

Reactive oxygen species

A lack of SDH activity results in increases in steady-state levels of O_2^- to H_2O_2 that could then form more powerful oxidants, such as hydroxyl radicals, through Haber–Weiss-driven Fenton chemistry as well as organic hydroperoxides capable of causing chronic metabolic oxidative stress (Slane *et al.* 2006, Spitz 2011, Owens *et al.* 2012). Chronic ROS exposure can result in oxidative damage to mitochondrial and cellular proteins, lipids, and nucleic acids. These normoxic ROS accelerate the DNA-damaging processes as a 'mutator phenotype', causing genomic instability, as well as an increase in glucose consumption and sensitivity to glucose deprivation-induced toxicity and slower growth rates. ROS are also involved in Ras–Raf–MEK signaling. Ras–Raf–MEK signaling activation causes the mediation of protection against apoptotic cell death induced by increased oxidative stress (Jiang *et al.* 2005). The activity of the ROS-generating enzyme Nox1 is

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required for VEGF, a potent stimulator of tumor angiogenesis (Rustin *et al*. 2002, Dudkina *et al*. 2005, Slane *et al*. 2006, Pan *et al*. 2009). Fliedner *et al*. (2012) detected elevated superoxide dismutase 2 expression in *SDHB*-derived PHEOs/PGLs that is an indirect evidence for increased ROS production and may reflect elevated oxidative stress.

Warburg effect

A lack of SDH activity and consequent other changes lead to the Warburg effect in *SDHx*-related tumors. Because metabolic control over the glycolytic rate can be applied at many steps in the glycolytic pathway (Dang *et al*. 1997, Gatenby & Gillies 2004), most studies in cancer support the hypothesis that control over glycolytic flux primarily resides at the transport and phosphorylation steps (upregulation of glucose transporters (notably GLUT1 and GLUT3) and HK2; Gatenby & Gillies 2004, Mathupala *et al*. 2009, Choi *et al*. 2013). HIFα enhances the glycolytic pathway by increasing target gene expression from GLUT1, GLUT3, through HK2 and pyruvate kinase variant M2 (PKM2) to lactate dehydrogenase-A (LDH-A) and other glycolytic and anabolic enzymes and metabolites (Osthus *et al*. 2000, Soga 2013). Some expression studies have not found the overexpression of GLUT1 in *SDHx*-related tumors (Favier *et al*. 2009, Lopez-Jimenez *et al*. 2010, Fliedner *et al*. 2012). Moreover, increased expression of *GLUT3* and *HK2* mRNAs observed in *SDHx*-related tumors (Favier *et al*. 2009, Fliedner *et al*. 2012) can explain the high sensitivity of [^{18}F]-FDG PET for *SDHx*-related tumors, mainly observed in *SDHB*-related PHEOs/PGLs (Timmers *et al*. 2007, 2009*b*, 2012, Zelinka *et al*. 2008, Taieb *et al*. 2009). Fliedner *et al*. (2012) detected the *M2* isoform of *PKM2* mRNA, which appeared to be possibly elevated in *SDHB*-mutant tumors. *PKM2* is generated by increased transcription and alternative splicing of the *PKM2* gene through a HIF1α and c-Myc-mediated process. *PKM2* catalyzes the final and also rate-limiting reaction in the glycolytic pathway and promotes tumorigenesis by regulating the Warburg effect. *PKM2* also possesses a positive feedback regulation toward HIF1α. *PKM2* interacts with HIF1α in the nucleus and functions as a transcriptional coactivator to enhance the expression of HIF1α target genes that promote the shift from OXPHOS to glycolytic metabolism (Luo & Semenza 2011, 2012, Luo *et al*. 2011). Also, overexpression of LDH-A has been found in *SDHx*-related tumors (Favier *et al*. 2009, Fliedner *et al*. 2012). In proliferating cancer cells, the majority of the pyruvate generated from glucose (>90%) is converted to lactate by LDH-A, where it is readily secreted into the extracellular environment. By converting pyruvate to lactate, LDH-A recovers the NAD^+ needed to maintain glycolysis and ATP production. This step is critical for the maintenance of tumor proliferation *in vivo* (Fantin *et al*. 2006, Jones & Thompson 2009). LDH-A may be upregulated by a high glycolytic flux through the carbohydrate-response elements (ChoREs) by binding HIF or myc products (Semenza 2002*a*,*b*, Walenta & Mueller-Klieser 2004). Moreover, both LDH-A and mitochondria activity are mutually regulated at the level of metabolites. They depend on the availability of pyruvate and on the $NADH:NAD^+$ ratio. The generation of lactate and the export of intracellular acid lead to an acidic tumor microenvironment, which is correlated with a poor prognosis and may facilitate tumor invasion and metastasis leading to the stimulation of cell migration and angiogenesis (Chiche *et al*. 2010, Vegran *et al*. 2011). Thus, activation of HIFα, c-myc, and other proteins stimulates many processes that result in the Warburg effect in these tumors (Vogelstein & Kinzler 2004, Deberardinis *et al*. 2008, Yuneva 2008, Jones & Thompson 2009, Gogvadze *et al*. 2010, Levine & Puzio-Kuter 2010, Cairns *et al*. 2011, Koppenol *et al*. 2011).

Glutamine metabolism

Tannahill *et al*. (2013) showed a dysfunctional TCA cycle pointed toward an alternative source of succinate. The microarray study showed a significantly higher concentration of glutamine transporter *SLC3A2* mRNA. Thus, substantial increases in succinate accumulation have been demonstrated through processes involving increased import and metabolism of glutamine (Tannahill *et al*. 2013). Therefore, we suggest that glutamine metabolism can be involved in *SDHx*-related tumors. Succinate can be derived from glutamine through anaplerosis by α-ketoglutarate. Recently, Imperiale *et al*. (2013) found significantly lower values of glutamate in *SDHx*-related tumors compared with other subtypes. These catabolic pathways are reversible and involve the removal of nitrogen as part of the mechanism that regulates nitrogen homeostasis; the carbon skeleton from glutaminolysis may eventually enter anabolic or anaplerotic processes (including the formation of nucleotides, lipids, and proteins; Yuneva 2008, Dang 2010, Eng & Abraham 2010).

Meng *et al*. (2010) observed that nitrogen source restriction repressed carbon metabolic pathways, including glucose utilization. Therefore, the interconversion between glutamine and α-ketoglutarate serves as the

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bridge connecting nitrogen and carbon metabolism. Thus, glutaminolysis and the Warburg effect become two integral parts of the cellular machinery to balance the carbon and nitrogen metabolism. Glutaminolysis also supports the production of molecules, such as GSH and NADPH, which protect cells from oxidative stress.

OXPHOS proteins

OXPHOS proteins include the electron transport chain components, ATP synthase, and the adenine nucleotide translocator. Information about other OXPHOS proteins besides complex II in *SDHx*-related tumors is limited. Favier *et al*. (2009) suggested a lower expression of OXPHOS protein complexes I–IV in *SDHx*- and *VHL*-related tumors than in PHEOs/PGLs harboring *NF1* and *RET* mutations, but complex V expression was relatively similar in all patients. Also, the activity of complexes II, III, or IV was found to be decreased in *SDHx*- and *VHL*-related PHEOs/PGLs, but the differences were smaller for complexes III and IV. In contrast, other groups showed that the activity of SDH or respiratory chain enzyme complex II is low in *SDHx*-related tumors and associated with increased activities of respiratory chain complexes I, III, and IV and citrate synthase. All these factors suggest a compensatory response to the lack of SDH activity (Fliedner *et al*. 2012, Rao *et al*. 2013). However, as shown by Rao *et al*. (2013), the apparently increased activity of complex I, III, IV, and citrate synthase in the *SDHx*-related tumors does not lead to a full restoration of ATP/ADP/AMP, because the concentration of ATP/ADP/AMP was consistently very low in all *SDHx*-related tumors. Rao *et al*. found positive relationships between mitochondrial complex II function, tumor ATP/ADP/AMP content, and tumor catecholamine contents, and suggested the possibility that differences in energy metabolism might also contribute to the lower tumor tissue catecholamine contents in cluster 1 than in cluster 2 tumors. Thus, increased activity of complex I, III, and IV may be a compensatory reaction to a lack of or decreased complex II activity in these tumors.

Thus, the generation of ROS as well as pseudohypoxia and succinate accumulation results in significant changes in key pathways: HIF, glycolysis, angiogenesis, genomic instability, increased cell cycle, and increased mutability.

In summary, increased ROS production has been suggested to contribute to tumorigenesis in *SDHB*-related tumors (Guzy *et al*. 2008, Goffrini *et al*. 2009, Huang & Lemire 2009). *SDHx* mutation-induced increases in ROS have recently been shown to cause genomic instability that may contribute to tumorigenesis (Slane *et al*. 2006, Owens *et al*. 2012). Second, accumulation of succinate leads to widespread changes, from stabilization of HIFα through inhibition of PHD to DNA hypermethylation, a process causing global changes in gene expression. This accumulation of succinate accompanies low fumarate in malignant *SDHB* tumors. This high succinate:fumarate ratio can be used as a predictor of malignancy in the future. Third, the specific catecholamine phenotype in *SDHx*-related tumors may be due to downregulation of HIF1α and upregulation of HIF2α. Fourth, not only glycolysis but also glutaminolysis may be involved in *SDHx*-related tumors.

Future treatment options to attack metabolic alterations in *SDHx*-related tumors

Understanding specific metabolic alterations characteristic and unique to *SDHx*-related PHEOs/PGLs and increasing availability and implementation of molecular profiling and metabolomics in clinical medicine opens new promising options for the use of multiple and personalized metabolic-specific molecular-targeted therapies in the near future, as originally suggested by Eng *et al*. (2003). Several key events involved in the pathogenesis of *SDHx*-related PHEOs/PGLs have been described, such as i) an increase in ROS production resulting in oxidative stress and stabilization of HIF1/2α and ii) accumulation of succinate which inhibits 2OG-dependent dioxygenases and causes hypermethylated and pseudohypoxic phenotypes. Identification of subgroups of specific molecular-metabolic phenotypes may be especially useful in personalized medicine. Furthermore, targeted therapies hold promise for the treatment of metastatic *SDHx*-related tumors. Thus, although outlined below separately, these approaches are viewed as tightly interconnected and should be combined when appropriate treatments or knowledge are available.

Restoration of SDH activity

An increase in the expression and stabilization of SDH proteins is crucial to prevent various metabolic dysregulations resulting from the absence of SDHB protein and therefore dysfunctional mitochondrial complex II in *SDHx*-related tumors. An increase in the expression and stabilization of SDH proteins is crucial to prevent various metabolic dysregulations resulting from the absence of SDHB protein and therefore dysfunctional mitochondrial

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complex II in SDHx-related tumors. Recently, Yang and colleagues demonstrated that the loss of SDHB function was due to a reduced half-life of mutant protein by rapid proteasome degradation. The authors found that histone deacetylase inhibitors (HDACi) inhibited proteasome degradation of SDHB-mutated protein resulting in its increased stabilization and activity (Yang *et al*. 2012). However, this approach, although of interest in the near future, cannot be applied to patients with nonsense *SDHx* mutations or *SDHx* gene deletions, because no protein is generated and the second allele is missing by the mechanism of loss of heterozygosity. Furthermore, it is expected that this approach will only partially increase the availability of mutated (and still dysfunctional) protein that will only improve mitochondrial function to a certain degree leading to persistent metabolic dysregulations (although to a lesser degree). Therefore, this therapy most likely will need to be combined with other therapeutic approaches.

Restoration of PHD activity

As described in our study, both succinate and ROS contribute to the inactivation of PHD and subsequent stabilization of the HIF1/2α signaling pathway. PHD action normally requires oxygen and α-ketoglutarate as co-substrates. PHD inactivation by succinate is competitive with α-ketoglutarate. Therefore, increasing the α-ketoglutarate:succinate ratio levels by treatment with α-ketoglutarate derivatives could critically affect PHD activity and decrease the stabilization of HIF1/2α (MacKenzie *et al*. 2007, Tennant *et al*. 2009, Jokilehto & Jaakkola 2010). Furthermore, esterified α-ketoglutarate induces apoptosis and inhibits tumor growth. These effects are independent of HIFα but dependent on the presence of PHD3 (Tennant & Gottlieb 2010).

Direct activation of PHD by the activator KRH102053 increases HIF1/2α hydroxylation and promotes its degradation (Choi *et al*. 2008, Nepal *et al*. 2011). Targeting HIF1/2α with their specific inhibitors (e.g. currently by either the direct inhibitor PX-478 or the indirect inhibitor PX-12; both targeted to HIF1α) has shown antitumoral activity in human tumor xenografts in mice and also seems to be promising for malignant PHEO/PGL (Welsh *et al*. 2003, 2004, Semenza 2007). However, currently there are no HIF2α inhibitors that would be preferable in the treatment of *SDHx*-related PHEO/PGL. Nevertheless, it is expected that these compounds will be introduced in the near future (Rogers *et al*. 2013).

Prevent ROS damage

A rationale for using antioxidants in HIF1/2α-driven tumors was recently provided by Gao *et al*. (2007), who examined the antitumorigenic effect of the antioxidant NAC. They reported that NAC treatment resulted in reduced HIF1α expression and inhibition of *in vivo* tumor formation in a HIF-driven model of tumorigenesis. Ni & Eng (2012) concluded that the lipid-soluble antioxidant α-tocopherol can selectively protect $SDHx^{var+}$ cells from oxidative damage and apoptosis resistance and rebalance the redox metabolites, NAD/NADH, which is a promising opportunity to prevent the development of tumors in patients with *SDHx* mutations. This concept is very unique, introducing prevention for the first time in the treatment of *SDHx* carriers. Thus, α-tocopherol, ascorbic acid, and HDACi could be administered over a long period and could serve as a novel therapeutic paradigm for preventing the development of *SDHx*-related PHEOs/PGLs (Ni & Eng 2012, Yang *et al*. 2012).

Heat shock protein 90 inhibitors

Malignant *SDHx*-related PHEO/PGL overexpresses heat shock protein 90 (HSP90), a molecular chaperone that assists in binding to HIF1/2α and promotes its stability by preventing ubiquitination and proteasomal degradation of HIF1/2α (Liu *et al*. 2007, Mahalingam *et al*. 2009, Semenza 2010). Thus, inhibitors of HSP90, such as geldanamycin, and analogs, such as 17-allylamino geldanamycin (17-AAG; tanespimycin), 17-dimethylaminoethylamino-17-demethoxygeldanamycin (alespimicin), or other new analogs, are promising therapeutic agents (Isaacs *et al*. 2002, Northcott *et al*. 2012). Giubelino *et al*. (2013) demonstrated the potent inhibition of proliferation and migration of PHEO cell lines and induced degradation of key Hsp90 clients by 17-AAG and ganetespib. They also showed the efficacy of 17-AAG and ganetespib in reducing metastatic burden and increasing survival in metastatic model of PHEO (Giubellino *et al*. 2013).

Glycolysis inhibition

In addition, when the TCA cycle is genetically compromised, as is the case in *SDHx*-related PHEO/PGL, glycolytic addiction of the tumor cells is ensured. These tumors are 'glucose addicts' as revealed by their almost 100% of positivity on [^{18}F]-FDG PET. This may prove to be an Achilles' heel of these tumors. Thus, strategies disrupting glycolytic mechanisms can be used in the future.

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A small-molecule inhibitor of GLUT1, such as WZB117 or STF-31, downregulates glycolysis and inhibits cancer cell growth *in vitro* and *in vivo* (Chan *et al*. 2011, Liu *et al*. 2012). In addition, dichloroacetate (DCA) and 3-bromopyruvate reverse cancer-specific aerobic glycolysis (Michelakis *et al*. 2008, Cardaci *et al*. 2012, El Sayed *et al*. 2012, Kluza *et al*. 2012, Kumar *et al*. 2012, Matsushita *et al*. 2012, Sutendra & Michelakis 2013, Sutendra *et al*. 2013). DCA downregulates pyruvate dehydrogenase kinase, which, under normal conditions, upregulates the glycolysis enzyme pyruvate dehydrogenase (Michelakis *et al*. 2008, Kluza *et al*. 2012, Kumar *et al*. 2012, Sutendra & Michelakis 2013, Sutendra *et al*. 2013), shifting metabolism from glycolysis to glucose oxidation and selectively inducing apoptosis in cancer cells (Xie *et al*. 2011). Furthermore, inhibitors of HK2 (Pedersen 2012, Yu *et al*. 2012) may also represent a novel therapeutic approach to malignant *SDHx*-related PHEO/PGL.

Disruption of pH regulators

In addition, activation of the HIF1α pathway enhances glycolytic metabolism and generates increased amounts of lactic and carbonic acids. This poses considerable cellular stress and requires a continuous regulation by several pH-regulating systems. It has been shown that disruption of these proteins may provide an effective avenue for future targeted therapies in different cancer models (Parks *et al*. 2013). However, several studies have shown a predominant expression of HIF2α over HIF1α in *SDH*-related tumors (Eisenhofer *et al*. 2004, Favier *et al*. 2009, Jochmanova *et al*. 2013), suggesting a leading role for HIF2α in *SDHx*-related tumorigenesis. Thus, the identification of subgroups of patients with preferential or combined activation of HIF1α or HIF1/2α, respectively, would help in the development of 'personalized' approaches in this type of therapy. In these patients, disrupting pH-regulating capacities and the export of lactic acid from tumor cells (by disrupting monocarboxylate transporters (MCTs)) could reduce glycolysis and growth rates. Additional strategies could be developed by disrupting glycolytic mechanisms.

Disruption of alternative signaling pathways

Additional treatment strategies could target abnormally functioning pathways, possibly in conjunction with targeting metabolic pathways. For example, the pseudo-hypoxic response and abnormal energy status of tumor cells activate kinase signaling pathways such as PI3kinase/AKT, RAS/RAF/ERK, and mTOR1/p70s6K, which leads to abnormal cell growth and a lack of apoptotic capacity (Abraham & Eng 2010, Choo *et al*. 2010, Nolting & Grossman 2012). Favier *et al*. (2012) showed that the mTOR pathway was potentially activated in half of PHEO/PGLs. Nolting *et al*. (2012) showed that combination treatment with dual NVP-BEZ235 (a PI3K/mTORC1 inhibitor) and lovastatin (an inhibitor of ERK signaling) had a significant additive effect in mice PHEO MPC and MTT cells and resulted in the inhibition of both AKT and mTORC1/p70S6K signaling without ERK upregulation. However, recently, Ghayee *et al*. (2013) suggested that the use of mTOR inhibitors alone for metastatic SDHB PHEOs/PGLs may not achieve good therapeutic efficacy in these patients.

Summary

Recent advances and insights into *SDHx*-related PHEOs/PGLs as tumors with significant changes in their metabolism may lead to major advances in the treatment of these tumors.

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

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Author contribution statement
A Vicha, D Taieb, and K Pacak contributed to the manuscript conception and design, data collection and interpretation, writing, editing, and final proof. K Pacak provided administrative support.

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References

Abraham RT & Eng CH 2010 A metabolic (re-)balancing act. *Molecular Cell* **38** 481–482. (doi:10.1016/j.molcel.2010.05.008)

Published by Bioscientifica Ltd.

Agger K, Christensen J, Cloos PA & Helin K 2008 The emerging functions of histone demethylases. *Current Opinion in Genetics & Development* **18** 159–168. (doi:10.1016/j.gde.2007.12.003)

Alston CL, Davison JE, Meloni F, van der Westhuizen FH, He L, Hornig-Do HT, Peet AC, Gissen P, Goffrini P, Ferrero I *et al.* 2012 Recessive germline SDHA and SDHB mutations causing leukodystrophy and isolated mitochondrial complex II deficiency. *Journal of Medical Genetics* **49** 569–577. (doi:10.1136/jmedgenet-2012-101146)

Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, Skoldberg F, Husebye ES, Eng C & Maher ER 2001 Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *American Journal of Human Genetics* **69** 49–54. (doi:10.1086/321282)

Astuti D, Hart-Holden N, Latif F, Lalloo F, Black GC, Lim C, Moran A, Grossman AB, Hodgson SV, Freemont A *et al.* 2003 Genetic analysis of mitochondrial complex II subunits SDHD, SDHB and SDHC in paraganglioma and phaeochromocytoma susceptibility. *Clinical Endocrinology* **59** 728–733. (doi:10.1046/j.1365-2265.2003.01914.x)

Astuti D, Morris M, Krona C, Abel F, Gentle D, Martinsson T, Kogner P, Neumann HP, Voutilainen R, Eng C *et al.* 2004 Investigation of the role of SDHB inactivation in sporadic phaeochromocytoma and neuroblastoma. *British Journal of Cancer* **91** 1835–1841. (doi:10.1038/sj.bjc.6602202)

Bardella C, Pollard PJ & Tomlinson I 2011 SDH mutations in cancer. *Biochimica et Biophysica Acta* **1807** 1432–1443. (doi:10.1016/j.bbabio.2011.07.003)

Bayley JP, Devilee P & Taschner PE 2005 The SDH mutation database: an online resource for succinate dehydrogenase sequence variants involved in pheochromocytoma, paraganglioma and mitochondrial complex II deficiency. *BMC Medical Genetics* **6** 39. (doi:10.1186/1471-2350-6-39)

Bayley JP, van Minderhout I, Weiss MM, Jansen JC, Oomen PH, Menko FH, Pasini B, Ferrando B, Wong N, Alpert LC *et al.* 2006 Mutation analysis of SDHB and SDHC: novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma. *BMC Medical Genetics* **7** 1. (doi:10.1186/1471-2350-7-1)

Baysal BE 2003 On the association of succinate dehydrogenase mutations with hereditary paraganglioma. *Trends in Endocrinology and Metabolism* **14** 453–459. (doi:10.1016/j.tem.2003.08.004)

Baysal BE 2004 Genomic imprinting and environment in hereditary paraganglioma. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* **129C** 85–90. (doi:10.1002/ajmg.c.30018)

Baysal BE 2008 Clinical and molecular progress in hereditary paraganglioma. *Journal of Medical Genetics* **45** 689–694. (doi:10.1136/jmg.2008.058560)

Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D, Bosch A, van der Mey A, Taschner PE, Rubinstein WS, Myers EN *et al.* 2000 Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science* **287** 848–851. (doi:10.1126/science.287.5454.848)

Benn DE, Gimenez-Roqueplo AP, Reilly JR, Bertherat J, Burgess J, Byth K, Croxson M, Dahia PL, Elston M, Gimm O *et al.* 2006 Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *Journal of Clinical Endocrinology and Metabolism* **91** 827–836. (doi:10.1210/jc.2005-1862)

Bensinger SJ & Christofk HR 2012 New aspects of the Warburg effect in cancer cell biology. *Seminars in Cell & Developmental Biology* **23** 352–361. (doi:10.1016/j.semcdb.2012.02.003)

Birch-Machin MA, Taylor RW, Cochran B, Ackrell BA & Turnbull DM 2000 Late-onset optic atrophy, ataxia, and myopathy associated with a mutation of a complex II gene. *Annals of Neurology* **48** 330–335. (doi:10.1002/1531-8249(200009)48:3<330::AID-ANA7>3.0.CO;2-A)

Branco-Price C, Zhang N, Schnelle M, Evans C, Katschinski DM, Liao D, Ellies L & Johnson RS 2012 Endothelial cell HIF-1α and HIF-2α differentially regulate metastatic success. *Cancer Cell* **21** 52–65. (doi:10.1016/j.ccr.2011.11.017)

Burnichon N, Rohmer V, Amar L, Herman P, Leboulleux S, Darrouzet V, Niccoli P, Gaillard D, Chabrier G, Chabolle F *et al.* 2009 The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. *Journal of Clinical Endocrinology and Metabolism* **94** 2817–2827. (doi:10.1210/jc.2008-2504)

Burnichon N, Briere JJ, Libe R, Vescovo L, Riviere J, Tissier F, Jouanno E, Jeunemaitre X, Benit P, Tzagoloff A *et al.* 2010 SDHA is a tumor suppressor gene causing paraganglioma. *Human Molecular Genetics* **19** 3011–3020. (doi:10.1093/hmg/ddq206)

Burnichon N, Vescovo L, Amar L, Libe R, de Reynies A, Venisse A, Jouanno E, Laurendeau I, Parfait B, Bertherat J *et al.* 2011 Integrative genomic analysis reveals somatic mutations in pheochromocytoma and paraganglioma. *Human Molecular Genetics* **20** 3974–3985. (doi:10.1093/hmg/ddr324)

Burnichon N, Buffet A, Parfait B, Letouze E, Laurendeau I, Loriot C, Pasmant E, Abermil N, Valeyrie-Allanore L, Bertherat J *et al.* 2012*a* Somatic NF1 inactivation is a frequent event in sporadic pheochromocytoma. *Human Molecular Genetics* **21** 5397–5405. (doi:10.1093/hmg/dds374)

Burnichon N, Cascon A, Schiavi F, Morales NP, Comino-Mendez I, Abermil N, Inglada-Perez L, de Cubas AA, Amar L, Barontini M *et al.* 2012*b* MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. *Clinical Cancer Research* **18** 2828–2837. (doi:10.1158/1078-0432.CCR-12-0160)

Cairns RA, Harris IS & Mak TW 2011 Regulation of cancer cell metabolism. *Nature Reviews. Cancer* **11** 85–95. (doi:10.1038/nrc2981)

Cardaci S, Desideri E & Ciriolo MR 2012 Targeting aerobic glycolysis: 3-bromopyruvate as a promising anticancer drug. *Journal of Bioenergetics and Biomembranes* **44** 17–29. (doi:10.1007/s10863-012-9422-7)

Cascon A & Tennant DA 2012 From transcriptional profiling to tumor biology in pheochromocytoma and paraganglioma. *Endocrine Pathology* **23** 15–20. (doi:10.1007/s12022-012-9195-x)

Cascon A, Landa I, Lopez-Jimenez E, Diez-Hernandez A, Buchta M, Montero-Conde C, Leskela S, Leandro-Garcia LJ, Leton R, Rodriguez-Antona C *et al.* 2008 Molecular characterisation of a common SDHB deletion in paraganglioma patients. *Journal of Medical Genetics* **45** 233–238. (doi:10.1136/jmg.2007.054965)

Castro-Vega LJ, Buffet A, de Cubas AA, Cascon A, Menara M, Khalifa E, Amar L, Azriel S, Bourdeau I, Chabre O *et al.* 2014 Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. *Human Molecular Genetics* **23** 2440–2446. (doi:10.1093/hmg/ddt639)

Cervera AM, Bayley JP, Devilee P & McCreath KJ 2009 Inhibition of succinate dehydrogenase dysregulates histone modification in mammalian cells. *Molecular Cancer* **8** 89. (doi:10.1186/1476-4598-8-89)

Chan DA, Sutphin PD, Nguyen P, Turcotte S, Lai EW, Banh A, Reynolds GE, Chi JT, Wu J, Solow-Cordero DE *et al.* 2011 Targeting GLUT1 and the Warburg effect in renal cell carcinoma by chemical synthetic lethality. *Science Translational Medicine* **3** 94ra70.

Chiavarina B, Martinez-Outschoorn UE, Whitaker-Menezes D, Howell A, Tanowitz HB, Pestell RG, Sotgia F & Lisanti MP 2012 Metabolic reprogramming and two-compartment tumor metabolism: opposing role(s) of HIF1α and HIF2α in tumor-associated fibroblasts and human breast cancer cells. *Cell Cycle* **11** 3280–3289. (doi:10.4161/cc.21643)

Chiche J, Brahimi-Horn MC & Pouyssegur J 2010 Tumour hypoxia induces a metabolic shift causing acidosis: a common feature in cancer. *Journal of Cellular and Molecular Medicine* **14** 771–794. (doi:10.1111/j.1582-4934.2009.00994.x)

Choi HJ, Song BJ, Gong YD, Gwak WJ & Soh Y 2008 Rapid degradation of hypoxia-inducible factor-1α by KRH102053, a new activator of prolyl hydroxylase 2. *British Journal of Pharmacology* **154** 114–125. (doi:10.1038/bjp.2008.70)

Choi J, Jung WH & Koo JS 2013 Metabolism-related proteins are differentially expressed according to the molecular subtype of invasive breast cancer defined by surrogate immunohistochemistry. *Pathobiology* **80** 41–52. (doi:10.1159/000339513)

Published by Bioscientifica Ltd.

Choo AY, Kim SG, Vander Heiden MG, Mahoney SJ, Vu H, Yoon SO, Cantley LC & Blenis J 2010 Glucose addiction of TSC null cells is caused by failed mTORC1-dependent balancing of metabolic demand with supply. *Molecular Cell* **38** 487–499. (doi:10.1016/j.molcel.2010.05.007)

Comino-Mendez I, Gracia-Aznarez FJ, Schiavi F, Landa I, Leandro-Garcia LJ, Leton R, Honrado E, Ramos-Medina R, Caronia D, Pita G *et al.* 2011 Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. *Nature Genetics* **43** 663–667. (doi:10.1038/ng.861)

Crona J, Delgado Verdugo A, Maharjan R, Stalberg P, Granberg D, Hellman P & Bjorklund P 2013 Somatic mutations in H-RAS in sporadic pheochromocytoma and paraganglioma identified by exome sequencing. *Journal of Clinical Endocrinology and Metabolism* **98** E1266–E1271. (doi:10.1210/jc.2012-4257)

Dahia PL 2013 The genetic landscape of pheochromocytomas and paragangliomas: somatic mutations take center stage. *Journal of Clinical Endocrinology and Metabolism* **98** 2679–2681. (doi:10.1210/jc.2013-2191)

Dahia PL, Ross KN, Wright ME, Hayashida CY, Santagata S, Barontini M, Kung AL, Sanso G, Powers JF, Tischler AS *et al.* 2005 A HIF1α regulatory loop links hypoxia and mitochondrial signals in pheochromocytomas. *PLoS Genetics* **1** 72–80. (doi:10.1371/journal.pgen.0010008)

Dang CV 2010 Glutaminolysis: supplying carbon or nitrogen or both for cancer cells? *Cell Cycle* **9** 3884–3886. (doi:10.4161/cc.9.19.13302)

Dang CV, Lewis BC, Dolde C, Dang G & Shim H 1997 Oncogenes in tumor metabolism, tumorigenesis, and apoptosis. *Journal of Bioenergetics and Biomembranes* **29** 345–354. (doi:10.1023/A:1022446730452)

Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC *et al.* 2009 Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* **462** 739–744. (doi:10.1038/nature08617)

Dann CE III & Bruick RK 2005 Dioxygenases as O_2-dependent regulators of the hypoxic response pathway. *Biochemical and Biophysical Research Communications* **338** 639–647. (doi:10.1016/j.bbrc.2005.08.140)

Deberardinis RJ, Sayed N, Ditsworth D & Thompson CB 2008 Brick by brick: metabolism and tumor cell growth. *Current Opinion in Genetics & Development* **18** 54–61. (doi:10.1016/j.gde.2008.02.003)

Dudkina NV, Eubel H, Keegstra W, Boekema EJ & Braun HP 2005 Structure of a mitochondrial supercomplex formed by respiratory-chain complexes I and III. *PNAS* **102** 3225–3229. (doi:10.1073/pnas.0408870102)

Eakin RT, Morgan LO, Gregg CT & Matwiyoff NA 1972 Carbon-13 nuclear magnetic resonance spectroscopy of living cells and their metabolism of a specifically labeled ^{13}C substrate. *FEBS Letters* **28** 259–264. (doi:10.1016/0014-5793(72)80726-9)

Eisenhofer G, Huynh TT, Pacak K, Brouwers FM, Walther MM, Linehan WM, Munson PJ, Mannelli M, Goldstein DS & Elkahloun AG 2004 Distinct gene expression profiles in norepinephrine- and epinephrine-producing hereditary and sporadic pheochromocytomas: activation of hypoxia-driven angiogenic pathways in von Hippel–Lindau syndrome. *Endocrine-Related Cancer* **11** 897–911. (doi:10.1677/erc.1.00838)

Eisenhofer G, Pacak K, Huynh TT, Qin N, Bratslavsky G, Linehan WM, Mannelli M, Friberg P, Grebe SK, Timmers HJ *et al.* 2011*a* Catecholamine metabolomic and secretory phenotypes in phaeochromocytoma. *Endocrine-Related Cancer* **18** 97–111. (doi:10.1677/ERC-10-0211)

Eisenhofer G, Lenders JW, Timmers H, Mannelli M, Grebe SK, Hofbauer LC, Bornstein SR, Tiebel O, Adams K, Bratslavsky G *et al.* 2011*b* Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. *Clinical Chemistry* **57** 411–420. (doi:10.1373/clinchem.2010.153320)

Eisenhofer G, Lenders JW, Siegert G, Bornstein SR, Friberg P, Milosevic D, Mannelli M, Linehan WM, Adams K, Timmers HJ *et al.* 2012 Plasma methoxytyramine: a novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. *European Journal of Cancer* **48** 1739–1749. (doi:10.1016/j.ejca.2011.07.016)

El Sayed SM, El-Magd RM, Shishido Y, Chung SP, Diem TH, Sakai T, Watanabe H, Kagami S & Fukui K 2012 3-Bromopyruvate antagonizes effects of lactate and pyruvate, synergizes with citrate and exerts novel anti-glioma effects. *Journal of Bioenergetics and Biomembranes* **44** 61–79. (doi:10.1007/s10863-012-9409-4)

Eltzschig HK, Eckle T & Grenz A 2009 PHD2 mutation and congenital erythrocytosis with paraganglioma. *New England Journal of Medicine* **360** 1361–1362 (author reply 1362). (doi:10.1056/NEJMc090088)

Eng CH & Abraham RT 2010 Glutaminolysis yields a metabolic by-product that stimulates autophagy. *Autophagy* **6** 968–970. (doi:10.4161/auto.6.7.13082)

Eng C, Kiuru M, Fernandez MJ & Aaltonen LA 2003 A role for mitochondrial enzymes in inherited neoplasia and beyond. *Nature Reviews. Cancer* **3** 193–202. (doi:10.1038/nrc1013)

Erlic Z, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, Mussig K, Muresan M, Schaffler A, Reisch N *et al.* 2009 Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. *Clinical Cancer Research* **15** 6378–6385. (doi:10.1158/1078-0432.CCR-09-1237)

Fantin VR, St-Pierre J & Leder P 2006 Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. *Cancer Cell* **9** 425–434. (doi:10.1016/j.ccr.2006.04.023)

Favier J & Gimenez-Roqueplo AP 2010 Pheochromocytomas: the (pseudo)-hypoxia hypothesis. *Best Practice & Research. Clinical Endocrinology & Metabolism* **24** 957–968. (doi:10.1016/j.beem.2010.10.004)

Favier J, Kempf H, Corvol P & Gasc JM 1999 Cloning and expression pattern of EPAS1 in the chicken embryo. Colocalization with tyrosine hydroxylase. *FEBS Letters* **462** 19–24. (doi:10.1016/S0014-5793(99)01476-3)

Favier J, Briere JJ, Burnichon N, Riviere J, Vescovo L, Benit P, Giscos-Douriez I, De Reynies A, Bertherat J, Badoual C *et al.* 2009 The Warburg effect is genetically determined in inherited pheochromocytomas. *PLoS ONE* **4** e7094. (doi:10.1371/journal.pone.0007094)

Favier J, Igaz P, Burnichon N, Amar L, Libe R, Badoual C, Tissier F, Bertherat J, Plouin PF, Jeunemaitre X *et al.* 2012 Rationale for anti-angiogenic therapy in pheochromocytoma and paraganglioma. *Endocrine Pathology* **23** 34–42. (doi:10.1007/s12022-011-9189-0)

Fliedner SMJ, Kaludercic N, Jiang X, Hansikova H, Hajkova Z, Sladkova J, Limpuangthip A, Backlund PS, Wesley R, Martiniova L *et al.* 2012 Warburg effect's manifestation in aggressive pheochromocytomas and paragangliomas: insights from a mouse cell model applied to human tumor tissue. *PLoS ONE* **7** e40949. (doi:10.1371/journal.pone.0040949)

Florczyk U, Czauderna S, Stachurska A, Tertil M, Nowak W, Kozakowska M, Poellinger L, Jozkowicz A, Loboda A & Dulak J 2011 Opposite effects of HIF-1α and HIF-2α on the regulation of IL-8 expression in endothelial cells. *Free Radical Biology & Medicine* **51** 1882–1892. (doi:10.1016/j.freeradbiomed.2011.08.023)

Franke K, Gassmann M & Wielockx B 2013 Erythrocytosis: the HIF pathway in control. *Blood* **122** 1122–1128. (doi:10.1182/blood-2013-01-478065)

Furlow PW, Percy MJ, Sutherland S, Bierl C, McMullin MF, Master SR, Lappin TR & Lee FS 2009 Erythrocytosis-associated HIF-2α mutations demonstrate a critical role for residues C-terminal to the hydroxylacceptor proline. *Journal of Biological Chemistry* **284** 9050–9058. (doi:10.1074/jbc.M808737200)

Gaal J, Burnichon N, Korpershoek E, Roncelin I, Bertherat J, Plouin PF, de Krijger RR, Gimenez-Roqueplo AP & Dinjens WN 2010 Isocitrate dehydrogenase mutations are rare in pheochromocytomas and paragangliomas. *Journal of Clinical Endocrinology and Metabolism* **95** 1274–1278. (doi:10.1210/jc.2009-2170)

Galan SR & Kann PH 2013 Genetics and molecular pathogenesis of pheochromocytoma and paraganglioma. *Clinical Endocrinology* **78** 165–175. (doi:10.1111/cen.12071)

Gao P, Zhang H, Dinavahi R, Li F, Xiang Y, Raman V, Bhujwalla ZM, Felsher DW, Cheng L, Pevsner J *et al.* 2007 HIF-dependent

Published by Bioscientifica Ltd.

antitumorigenic effect of antioxidants *in vivo*. *Cancer Cell* **12** 230–238. (doi:10.1016/j.ccr.2007.08.004)

Gatenby RA & Gillies RJ 2004 Why do cancers have high aerobic glycolysis? *Nature Reviews. Cancer* **4** 891–899. (doi:10.1038/nrc1478)

Ghayee HK, Giubellino A, Click A, Kapur P, Christie A, Xie XJ, Martucci V, Shay JW, Souza RF & Pacak K 2013 Phospho-mTOR is not upregulated in metastatic SDHB paragangliomas. *European Journal of Clinical Investigation* **43** 970–977. (doi:10.1111/eci.12127)

Gill AJ, Pachter NS, Clarkson A, Tucker KM, Winship IM, Benn DE, Robinson BG & Clifton-Bligh RJ 2011 Renal tumors and hereditary pheochromocytoma–paraganglioma syndrome type 4. *New England Journal of Medicine* **364** 885–886. (doi:10.1056/NEJMc1012357)

Gimenez-Roqueplo AP, Favier J, Rustin P, Mourad JJ, Plouin PF, Corvol P, Rotig A & Jeunemaitre X 2001 The R22X mutation of the SDHD gene in hereditary paraganglioma abolishes the enzymatic activity of complex II in the mitochondrial respiratory chain and activates the hypoxia pathway. *American Journal of Human Genetics* **69** 1186–1197. (doi:10.1086/324413)

Gimenez-Roqueplo AP, Favier J, Rustin P, Rieubland C, Kerlan V, Plouin PF, Rotig A & Jeunemaitre X 2002 Functional consequences of a SDHB gene mutation in an apparently sporadic pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **87** 4771–4774. (doi:10.1210/jc.2002-020525)

Gimenez-Roqueplo AP, Favier J, Rustin P, Rieubland C, Crespin M, Nau V, Khau Van Kien P, Corvol P, Plouin PF & Jeunemaitre X 2003 Mutations in the SDHB gene are associated with extra-adrenal and/or malignant phaeochromocytomas. *Cancer Research* **63** 5615–5621.

Gimenez-Roqueplo AP, Dahia PL & Robledo M 2012 An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. *Hormone and Metabolic Research* **44** 328–333. (doi:10.1055/s-0031-1301302)

Giubellino A, Sourbier C, Lee MJ, Scroggins B, Bullova P, Landau M, Ying W, Neckers L, Trepel JB & Pacak K 2013 Targeting heat shock protein 90 for the treatment of malignant pheochromocytoma. *PLoS ONE* **8** e56083. (doi:10.1371/journal.pone.0056083)

Goffrini P, Ercolino T, Panizza E, Giache V, Cavone L, Chiarugi A, Dima V, Ferrero I & Mannelli M 2009 Functional study in a yeast model of a novel succinate dehydrogenase subunit B gene germline missense mutation (C191Y) diagnosed in a patient affected by a glomus tumor. *Human Molecular Genetics* **18** 1860–1868. (doi:10.1093/hmg/ddp102)

Gogvadze V, Zhivotovsky B & Orrenius S 2010 The Warburg effect and mitochondrial stability in cancer cells. *Molecular Aspects of Medicine* **31** 60–74. (doi:10.1016/j.mam.2009.12.004)

Gottlieb E & Tomlinson IP 2005 Mitochondrial tumour suppressors: a genetic and biochemical update. *Nature Reviews. Cancer* **5** 857–866. (doi:10.1038/nrc1737)

Guzy RD, Sharma B, Bell E, Chandel NS & Schumacker PT 2008 Loss of the SdhB, but not the SdhA, subunit of complex II triggers reactive oxygen species-dependent hypoxia-inducible factor activation and tumorigenesis. *Molecular and Cellular Biology* **28** 718–731. (doi:10.1128/MCB.01338-07)

Hanahan D & Weinberg RA 2000 The hallmarks of cancer. *Cell* **100** 57–70. (doi:10.1016/S0092-8674(00)81683-9)

Hanahan D & Weinberg RA 2011 Hallmarks of cancer: the next generation. *Cell* **144** 646–674. (doi:10.1016/j.cell.2011.02.013)

Hao HX, Khalimonchuk O, Schraders M, Dephoure N, Bayley JP, Kunst H, Devilee P, Cremers CW, Schiffman JD, Bentz BG *et al*. 2009 SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. *Science* **325** 1139–1142. (doi:10.1126/science.1175689)

Hewitson KS, McNeill LA, Elkins JM & Schofield CJ 2003 The role of iron and 2-oxoglutarate oxygenases in signalling. *Biochemical Society Transactions* **31** 510–515. (doi:10.1042/BST0310510)

Hobert JA, Mester JL, Moline J & Eng C 2012 Elevated plasma succinate in PTEN, SDHB, and SDHD mutation-positive individuals. *Genetics in Medicine* **14** 616–619. (doi:10.1038/gim.2011.63)

Holmquist-Mengelbier L, Fredlund E, Lofstedt T, Noguera R, Navarro S, Nilsson H, Pietras A, Vallon-Christersson J, Borg A, Gradin K *et al*. 2006 Recruitment of HIF-1α and HIF-2α to common target genes is differentially regulated in neuroblastoma: HIF-2α promotes an aggressive phenotype. *Cancer Cell* **10** 413–423. (doi:10.1016/j.ccr.2006.08.026)

Horvath R, Abicht A, Holinski-Feder E, Laner A, Gempel K, Prokisch H, Lochmuller H, Klopstock T & Jaksch M 2006 Leigh syndrome caused by mutations in the flavoprotein (Fp) subunit of succinate dehydrogenase (SDHA). *Journal of Neurology, Neurosurgery, and Psychiatry* **77** 74–76. (doi:10.1136/jnnp.2005.067041)

Huang J & Lemire BD 2009 Mutations in the *C. elegans* succinate dehydrogenase iron–sulfur subunit promote superoxide generation and premature aging. *Journal of Molecular Biology* **387** 559–569. (doi:10.1016/j.jmb.2009.02.028)

Imperiale A, Moussallieh FM, Sebag F, Brunaud L, Barlier A, Elbayed K, Bachellier P, Goichot B, Pacak K, Namer IJ *et al*. 2013 A new specific succinate–glutamate metabolomic hallmark in sdhx-related paragangliomas. *PLoS ONE* **8** e80539. (doi:10.1371/journal.pone.0080539)

Isaacs JS, Jung YJ, Mimnaugh EG, Martinez A, Cuttitta F & Neckers LM 2002 Hsp90 regulates a von Hippel Lindau-independent hypoxia-inducible factor-1α-degradative pathway. *Journal of Biological Chemistry* **277** 29936–29944. (doi:10.1074/jbc.M204733200)

Isaacs JS, Jung YJ, Mole DR, Lee S, Torres-Cabala C, Chung YL, Merino M, Trepel J, Zbar B, Toro J *et al*. 2005 HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: novel role of fumarate in regulation of HIF stability. *Cancer Cell* **8** 143–153. (doi:10.1016/j.ccr.2005.06.017)

Jiang S & Dahia PL 2011 Minireview: The busy road to pheochromocytomas and paragangliomas has a new member, TMEM127. *Endocrinology* **152** 2133–2140. (doi:10.1210/en.2011-0052)

Jiang H, Zhang L, Koubi D, Kuo J, Groc L, Rodriguez AI, Hunter TJ, Tang S, Lazarovici P, Gautam SC *et al*. 2005 Roles of Ras–Erk in apoptosis of PC12 cells induced by trophic factor withdrawal or oxidative stress. *Journal of Molecular Neuroscience* **25** 133–140. (doi:10.1385/JMN:25:2:133)

Jochmanova I, Yang C, Zhuang Z & Pacak K 2013 Hypoxia-inducible factor signaling in pheochromocytoma: turning the rudder in the right direction. *Journal of the National Cancer Institute* **105** 1270–1283. (doi:10.1093/jnci/djt201)

Jokilehto T & Jaakkola PM 2010 The role of HIF prolyl hydroxylases in tumour growth. *Journal of Cellular and Molecular Medicine* **14** 758–770. (doi:10.1111/j.1582-4934.2010.01030.x)

Jones RG & Thompson CB 2009 Tumor suppressors and cell metabolism: a recipe for cancer growth. *Genes and Development* **23** 537–548. (doi:10.1101/gad.1756509)

Kaelin WG Jr & McKnight SL 2013 Influence of metabolism on epigenetics and disease. *Cell* **153** 56–69. (doi:10.1016/j.cell.2013.03.004)

Kaelin WG Jr & Ratcliffe PJ 2008 Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Molecular Cell* **30** 393–402. (doi:10.1016/j.molcel.2008.04.009)

Keith B, Johnson RS & Simon MC 2012 HIF1α and HIF2α: sibling rivalry in hypoxic tumour growth and progression. *Nature Reviews. Cancer* **12** 9–22. (doi:10.1038/nrc3183)

Khan MN, Bhattacharyya T, Andrikopoulos P, Esteban MA, Barod R, Connor T, Ashcroft M, Maxwell PH & Kiriakidis S 2011 Factor inhibiting HIF (FIH-1) promotes renal cancer cell survival by protecting cells from HIF-1α-mediated apoptosis. *British Journal of Cancer* **104** 1151–1159. (doi:10.1038/bjc.2011.73)

Killian JK, Kim SY, Miettinen M, Smith C, Merino M, Tsokos M, Quezado M, Smith WI Jr, Jahromi MS, Xekouki P *et al*. 2013 Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor. *Cancer Discovery* **3** 648–657. (doi:10.1158/2159-8290.CD-13-0092)

Published by Bioscientifica Ltd.

King A, Selak MA & Gottlieb E 2006 Succinate dehydrogenase and fumarate hydratase: linking mitochondrial dysfunction and cancer. *Oncogene* **25** 4675–4682. (doi:10.1038/sj.onc.1209594)

Kluza J, Corazao-Rozas P, Touil Y, Jendoubi M, Maire C, Guerreschi P, Jonneaux A, Ballot C, Balayssac S, Valable S *et al.* 2012 Inactivation of the HIF-1α/PDK3 signaling axis drives melanoma toward mitochondrial oxidative metabolism and potentiates the therapeutic activity of pro-oxidants. *Cancer Research* **72** 5035–5047. (doi:10.1158/0008-5472.CAN-12-0979)

Koh MY, Lemos R Jr, Liu X & Powis G 2011 The hypoxia-associated factor switches cells from HIF-1α- to HIF-2α-dependent signaling promoting stem cell characteristics, aggressive tumor growth and invasion. *Cancer Research* **71** 4015–4027. (doi:10.1158/0008-5472.CAN-10-4142)

Koppenol WH, Bounds PL & Dang CV 2011 Otto Warburg's contributions to current concepts of cancer metabolism. *Nature Reviews. Cancer* **11** 325–337. (doi:10.1038/nrc3038)

Korpershoek E, Favier J, Gaal J, Burnichon N, van Gessel B, Oudijk L, Badoual C, Gadessaud N, Venisse A, Bayley JP *et al.* 2011 SDHA immunohistochemistry detects germline SDHA gene mutations in apparently sporadic paragangliomas and pheochromocytomas. *Journal of Clinical Endocrinology and Metabolism* **96** E1472–E1476. (doi:10.1210/jc.2011-1043)

Krejci A 2012 Metabolic sensors and their interplay with cell signalling and transcription. *Biochemical Society Transactions* **40** 311–323. (doi:10.1042/BST20110767)

Kumar A, Kant S & Singh SM 2012 Novel molecular mechanisms of antitumor action of dichloroacetate against T cell lymphoma: implication of altered glucose metabolism, pH homeostasis and cell survival regulation. *Chemico-Biological Interactions* **199** 29–37. (doi:10.1016/j.cbi.2012.06.005)

Ladroue C, Carcenac R, Leporrier M, Gad S, Le Hello C, Galateau-Salle F, Feunteun J, Pouyssegur J, Richard S & Gardie B 2008 PHD2 mutation and congenital erythrocytosis with paraganglioma. *New England Journal of Medicine* **359** 2685–2692. (doi:10.1056/NEJMoa0806277)

Lando D, Peet DJ, Gorman JJ, Whelan DA, Whitelaw ML & Bruick RK 2002 FIH-1 is an asparaginyl hydroxylase enzyme that regulates the transcriptional activity of hypoxia-inducible factor. *Genes and Development* **16** 1466–1471. (doi:10.1101/gad.991402)

Latif F, Duh FM, Gnarra J, Tory K, Kuzmin I, Yao M, Stackhouse T, Modi W, Geil L, Schmidt L *et al.* 1993 von Hippel–Lindau syndrome: cloning and identification of the plasma membrane Ca(++)-transporting ATPase isoform 2 gene that resides in the von Hippel–Lindau gene region. *Cancer Research* **53** 861–867.

Lee S, Nakamura E, Yang H, Wei W, Linggi MS, Sajan MP, Farese RV, Freeman RS, Carter BD, Kaelin WG Jr *et al.* 2005 Neuronal apoptosis linked to EglN3 prolyl hydroxylase and familial pheochromocytoma genes: developmental culling and cancer. *Cancer Cell* **8** 155–167. (doi:10.1016/j.ccr.2005.06.015)

Lenders JW, Eisenhofer G, Mannelli M & Pacak K 2005 Phaeochromocytoma. *Lancet* **366** 665–675. (doi:10.1016/S0140-6736(05)67139-5)

Lendvai N, Pawlosky R, Bullova P, Eisenhofer G, Patocs A, Veech RL & Pacak K 2014 Succinate-to-fumarate ratio as a new metabolic marker to detect the presence of SDHB/D-related paraganglioma: initial experimental and *ex vivo* findings. *Endocrinology* **155** 27–32. (doi:10.1210/en.2013-1549)

Letouze E, Martinelli C, Loriot C, Burnichon N, Abermil N, Ottolenghi C, Janin M, Menara M, Nguyen AT, Benit P *et al.* 2013 SDH mutations establish a hypermethylator phenotype in paraganglioma. *Cancer Cell* **23** 739–752. (doi:10.1016/j.ccr.2013.04.018)

Levine AJ & Puzio-Kuter AM 2010 The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. *Science* **330** 1340–1344. (doi:10.1126/science.1193494)

Levitas A, Muhammad E, Harel G, Saada A, Caspi VC, Manor E, Beck JC, Sheffield V & Parvari R 2010 Familial neonatal isolated cardiomyopathy caused by a mutation in the flavoprotein subunit of succinate dehydrogenase. *European Journal of Human Genetics* **18** 1160–1165. (doi:10.1038/ejhg.2010.83)

Linehan WM & Rouault TA 2013 Molecular pathways: fumarate hydratase-deficient kidney cancer – targeting the Warburg effect in cancer. *Clinical Cancer Research* **19** 3345–3352. (doi:10.1158/1078-0432.CCR-13-0304)

Liu YV, Baek JH, Zhang H, Diez R, Cole RN & Semenza GL 2007 RACK1 competes with HSP90 for binding to HIF-1α and is required for O(2)-independent and HSP90 inhibitor-induced degradation of HIF-1α. *Molecular Cell* **25** 207–217. (doi:10.1016/j.molcel.2007.01.001)

Liu Y, Cao Y, Zhang W, Bergmeier S, Qian Y, Akbar H, Colvin R, Ding J, Tong L, Wu S *et al.* 2012 A small-molecule inhibitor of glucose transporter 1 downregulates glycolysis, induces cell-cycle arrest, and inhibits cancer cell growth *in vitro* and *in vivo*. *Molecular Cancer Therapeutics* **11** 1672–1682. (doi:10.1158/1535-7163.MCT-12-0131)

Lopez-Jimenez E, Gomez-Lopez G, Leandro-Garcia LJ, Munoz I, Schiavi F, Montero-Conde C, de Cubas AA, Ramires R, Landa I, Leskela S *et al.* 2010 Research resource: Transcriptional profiling reveals different pseudohypoxic signatures in SDHB and VHL-related pheochromocytomas. *Molecular Endocrinology* **24** 2382–2391. (doi:10.1210/me.2010-0256)

Lorenzo FR, Yang C, Ng Tang Fui M, Vankayalapati H, Zhuang Z, Huynh T, Grossmann M, Pacak K & Prchal JT 2012 A novel EPAS1/HIF2A germline mutation in a congenital polycythemia with paraganglioma. *Journal of Molecular Medicine* **91** 507–512. (doi:10.1007/s00109-012-0967-z)

Luo W & Semenza GL 2011 Pyruvate kinase M2 regulates glucose metabolism by functioning as a coactivator for hypoxia-inducible factor 1 in cancer cells. *Oncotarget* **2** 551–556.

Luo W & Semenza GL 2012 Emerging roles of PKM2 in cell metabolism and cancer progression. *Trends in Endocrinology and Metabolism* **23** 560–566. (doi:10.1016/j.tem.2012.06.010)

Luo W, Hu H, Chang R, Zhong J, Knabel M, O'Meally R, Cole RN, Pandey A & Semenza GL 2011 Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. *Cell* **145** 732–744. (doi:10.1016/j.cell.2011.03.054)

MacKenzie ED, Selak MA, Tennant DA, Payne LJ, Crosby S, Frederiksen CM, Watson DG & Gottlieb E 2007 Cell-permeating α-ketoglutarate derivatives alleviate pseudohypoxia in succinate dehydrogenase-deficient cells. *Molecular and Cellular Biology* **27** 3282–3289. (doi:10.1128/MCB.01927-06)

Mahalingam D, Swords R, Carew JS, Nawrocki ST, Bhalla K & Giles FJ 2009 Targeting HSP90 for cancer therapy. *British Journal of Cancer* **100** 1523–1529. (doi:10.1038/sj.bjc.6605066)

Maher ER & Eng C 2002 The pressure rises: update on the genetics of phaeochromocytoma. *Human Molecular Genetics* **11** 2347–2354. (doi:10.1093/hmg/11.20.2347)

Mahon PC, Hirota K & Semenza GL 2001 FIH-1: a novel protein that interacts with HIF-1α and VHL to mediate repression of HIF-1 transcriptional activity. *Genes and Development* **15** 2675–2686. (doi:10.1101/gad.924501)

Majmundar AJ, Wong WJ & Simon MC 2010 Hypoxia-inducible factors and the response to hypoxic stress. *Molecular Cell* **40** 294–309. (doi:10.1016/j.molcel.2010.09.022)

Mathupala SP, Ko YH & Pedersen PL 2009 Hexokinase-2 bound to mitochondria: cancer's stygian link to the "Warburg Effect" and a pivotal target for effective therapy. *Seminars in Cancer Biology* **19** 17–24. (doi:10.1016/j.semcancer.2008.11.006)

Matsushita K, Uchida K, Saigusa S, Ide S, Hashimoto K, Koike Y, Otake K, Inoue M, Tanaka K & Kusunoki M 2012 Glycolysis inhibitors as a potential therapeutic option to treat aggressive neuroblastoma expressing GLUT1. *Journal of Pediatric Surgery* **47** 1323–1330. (doi:10.1016/j.jpedsurg.2011.12.007)

Meng M, Chen S, Lao T, Liang D & Sang N 2010 Nitrogen anabolism underlies the importance of glutaminolysis in proliferating cells. *Cell Cycle* **9** 3921–3932. (doi:10.4161/cc.9.19.13139)

Michelakis ED, Webster L & Mackey JR 2008 Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer. *British Journal of Cancer* **99** 989–994. (doi:10.1038/sj.bjc.6604554)

Published by Bioscientifica Ltd.

Mole DR, Blancher C, Copley RR, Pollard PJ, Gleadle JM, Ragoussis J & Ratcliffe PJ 2009 Genome-wide association of hypoxia-inducible factor (HIF)-1α and HIF-2α DNA binding with expression profiling of hypoxia-inducible transcripts. *Journal of Biological Chemistry* **284** 16767–16775. (doi:10.1074/jbc.M901790200)

Mulligan LM, Kwok JB, Healey CS, Elsdon MJ, Eng C, Gardner E, Love DR, Mole SE, Moore JK, Papi L *et al.* 1993 Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. *Nature* **363** 458–460. (doi:10.1038/363458a0)

Nakajima EC & Van Houten B 2013 Metabolic symbiosis in cancer: refocusing the Warburg lens. *Molecular Carcinogenesis* **52** 329–337. (doi:10.1002/mc.21863)

van Nederveen FH, Gaal J, Favier J, Korpershoek E, Oldenburg RA, de Bruyn EM, Sleddens HF, Derkx P, Riviere J, Dannenberg H *et al.* 2009 An immunohistochemical procedure to detect patients with paraganglioma and phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. *Lancet Oncology* **10** 764–771. (doi:10.1016/S1470-2045(09)70164-0)

Nepal M, Gong YD, Park YR & Soh Y 2011 An activator of PHD2, KRH102140, decreases angiogenesis via inhibition of HIF-1α. *Cell Biochemistry and Function* **29** 126–134. (doi:10.1002/cbf.1732)

Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Altehoefer C, Zerres K *et al.* 2002 Germ-line mutations in nonsyndromic pheochromocytoma. *New England Journal of Medicine* **346** 1459–1466. (doi:10.1056/NEJMoa020152)

Ni Y & Eng C 2012 Vitamin E protects against lipid peroxidation and rescues tumorigenic phenotypes in Cowden/Cowden-like patient-derived lymphoblast cells with germline SDHx variants. *Clinical Cancer Research* **18** 4954–4961. (doi:10.1158/1078-0432.CCR-12-1055)

Ni Y, Zbuk KM, Sadler T, Patocs A, Lobo G, Edelman E, Platzer P, Orloff MS, Waite KA & Eng C 2008 Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. *American Journal of Human Genetics* **83** 261–268. (doi:10.1016/j.ajhg.2008.07.011)

Ni Y, He X, Chen J, Moline J, Mester J, Orloff MS, Ringel MD & Eng C 2012 Germline SDHx variants modify breast and thyroid cancer risks in Cowden and Cowden-like syndrome via FAD/NAD-dependant destabilization of p53. *Human Molecular Genetics* **21** 300–310. (doi:10.1093/hmg/ddr459)

Niemann S & Muller U 2000 Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nature Genetics* **26** 268–270. (doi:10.1038/81551)

Nilsson H, Jogi A, Beckman S, Harris AL, Poellinger L & Pahlman S 2005 HIF-2α expression in human fetal paraganglia and neuroblastoma: relation to sympathetic differentiation, glucose deficiency, and hypoxia. *Experimental Cell Research* **303** 447–456. (doi:10.1016/j.yexcr.2004.10.003)

Nolting S & Grossman AB 2012 Signaling pathways in pheochromocytomas and paragangliomas: prospects for future therapies. *Endocrine Pathology* **23** 21–33. (doi:10.1007/s12022-012-9199-6)

Nolting S, Garcia E, Alusi G, Giubellino A, Pacak K, Korbonits M & Grossman AB 2012 Combined blockade of signalling pathways shows marked anti-tumour potential in phaeochromocytoma cell lines. *Journal of Molecular Endocrinology* **49** 79–96. (doi:10.1530/JME-12-0028)

Northcott PA, Shih DJ, Remke M, Cho YJ, Kool M, Hawkins C, Eberhart CG, Dubuc A, Guettouche T, Cardentey Y *et al.* 2012 Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. *Acta Neuropathologica* **123** 615–626. (doi:10.1007/s00401-011-0899-7)

Osthus RC, Shim H, Kim S, Li Q, Reddy R, Mukherjee M, Xu Y, Wonsey D, Lee LA & Dang CV 2000 Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. *Journal of Biological Chemistry* **275** 21797–21800. (doi:10.1074/jbc.C000023200)

Owens KM, Aykin-Burns N, Dayal D, Coleman MC, Domann FE & Spitz DR 2012 Genomic instability induced by mutant succinate dehydrogenase subunit D (SDHD) is mediated by $O_2(-\cdot)$ and H_2O_2. *Free Radical Biology & Medicine* **52** 160–166. (doi:10.1016/j.freeradbiomed.2011.10.435)

Pan JS, Hong MZ & Ren JL 2009 Reactive oxygen species: a double-edged sword in oncogenesis. *World Journal of Gastroenterology* **15** 1702–1707. (doi:10.3748/wjg.15.1702)

Papaspyrou K, Mewes T, Rossmann H, Fottner C, Schneider-Raetzke B, Bartsch O, Schreckenberger M, Lackner KJ, Amedee RG & Mann WJ 2012 Head and neck paragangliomas: Report of 175 patients (1989–2010). *Head & Neck* **34** 632–637. (doi:10.1002/hed.21790)

Parfait B, Chretien D, Rotig A, Marsac C, Munnich A & Rustin P 2000 Compound heterozygous mutations in the flavoprotein gene of the respiratory chain complex II in a patient with Leigh syndrome. *Human Genetics* **106** 236–243. (doi:10.1007/s004390051033)

Parks SK, Chiche J & Pouyssegur J 2013 Disrupting proton dynamics and energy metabolism for cancer therapy. *Nature Reviews. Cancer* **13** 611–623. (doi:10.1038/nrc3579)

Patel SA & Simon MC 2008 Biology of hypoxia-inducible factor-2α in development and disease. *Cell Death and Differentiation* **15** 628–634. (doi:10.1038/cdd.2008.17)

Pedersen PL 2012 3-Bromopyruvate (3BP) a fast acting, promising, powerful, specific, and effective "small molecule" anti-cancer agent taken from labside to bedside: introduction to a special issue. *Journal of Bioenergetics and Biomembranes* **44** 1–6. (doi:10.1007/s10863-012-9425-4)

Pollard PJ, Briere JJ, Alam NA, Barwell J, Barclay E, Wortham NC, Hunt T, Mitchell M, Olpin S, Moat SJ *et al.* 2005 Accumulation of Krebs cycle intermediates and over-expression of HIF1α in tumours which result from germline FH and SDH mutations. *Human Molecular Genetics* **14** 2231–2239. (doi:10.1093/hmg/ddi227)

Pollard PJ, El-Bahrawy M, Poulsom R, Elia G, Killick P, Kelly G, Hunt T, Jeffery R, Seedhar P, Barwell J *et al.* 2006 Expression of HIF-1α, HIF-2α (EPAS1), and their target genes in paraganglioma and pheochromocytoma with VHL and SDH mutations. *Journal of Clinical Endocrinology and Metabolism* **91** 4593–4598. (doi:10.1210/jc.2006-0920)

Powers JF, Evinger MJ, Zhi J, Picard KL & Tischler AS 2007 Pheochromocytomas in Nf1 knockout mice express a neural progenitor gene expression profile. *Neuroscience* **147** 928–937. (doi:10.1016/j.neuroscience.2007.05.008)

Qin Y, Yao L, King EE, Buddavarapu K, Lenci RE, Chocron ES, Lechleiter JD, Sass M, Aronin N, Schiavi F *et al.* 2010 Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. *Nature Genetics* **42** 229–233. (doi:10.1038/ng.533)

Rankin EB, Biju MP, Liu Q, Unger TL, Rha J, Johnson RS, Simon MC, Keith B & Haase VH 2007 Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin *in vivo*. *Journal of Clinical Investigation* **117** 1068–1077. (doi:10.1172/JCI30117)

Rao JU, Engelke UF, Rodenburg RJ, Wevers RA, Pacak K, Eisenhofer G, Qin N, Kusters B, Goudswaard AG, Lenders JW *et al.* 2013 Genotype-specific abnormalities in mitochondrial function associate with distinct profiles of energy metabolism and catecholamine content in pheochromocytoma and paraganglioma. *Clinical Cancer Research* **19** 3787–3795. (doi:10.1158/1078-0432.CCR-12-3922)

Rapizzi E, Ercolino T, Canu L, Giache V, Francalanci M, Pratesi C, Valeri A & Mannelli M 2012 Mitochondrial function and content in pheochromocytoma/paraganglioma of succinate dehydrogenase mutation carriers. *Endocrine-Related Cancer* **19** 261–269. (doi:10.1530/ERC-11-0263)

Rogers JL, Bayeh L, Scheuermann TH, Longgood J, Key J, Naidoo J, Melito L, Shokri C, Frantz DE, Bruick RK *et al.* 2013 Development of inhibitors of the PAS-B domain of the HIF-2α transcription factor. *Journal of Medicinal Chemistry* **56** 1739–1747. (doi:10.1021/jm301847z)

Rustin P, Munnich A & Rotig A 2002 Succinate dehydrogenase and human diseases: new insights into a well-known enzyme. *European Journal of Human Genetics* **10** 289–291. (doi:10.1038/sj.ejhg.5200793)

Sandgren J, Diaz de Stahl T, Andersson R, Menzel U, Piotrowski A, Nord H, Backdahl M, Kiss NB, Brauckhoff M, Komorowski J *et al.* 2010 Recurrent

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genomic alterations in benign and malignant pheochromocytomas and paragangliomas revealed by whole-genome array comparative genomic hybridization analysis. *Endocrine-Related Cancer* **17** 561–579. (doi:10.1677/ERC-09-0310)

Schiavi F, Boedeker CC, Bausch B, Peczkowska M, Gomez CF, Strassburg T, Pawlu C, Buchta M, Salzmann M, Hoffmann MM *et al.* 2005 Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. *Journal of the American Medical Association* **294** 2057–2063. (doi:10.1001/jama.294.16.2057)

Schlisio S, Kenchappa RS, Vredeveld LC, George RE, Stewart R, Greulich H, Shahriari K, Nguyen NV, Pigny P, Dahia PL *et al.* 2008 The kinesin KIF1Bβ acts downstream from EglN3 to induce apoptosis and is a potential 1p36 tumor suppressor. *Genes and Development* **22** 884–893. (doi:10.1101/gad.1648608)

Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, Pan Y, Simon MC, Thompson CB & Gottlieb E 2005 Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α prolyl hydroxylase. *Cancer Cell* **7** 77–85. (doi:10.1016/j.ccr.2004.11.022)

Semenza G 2002*a* Signal transduction to hypoxia-inducible factor 1. *Biochemical Pharmacology* **64** 993–998. (doi:10.1016/S0006-2952(02)01168-1)

Semenza GL 2002*b* HIF-1 and tumor progression: pathophysiology and therapeutics. *Trends in Molecular Medicine* **8** S62–S67. (doi:10.1016/S1471-4914(02)02317-1)

Semenza GL 2007 Evaluation of HIF-1 inhibitors as anticancer agents. *Drug Discovery Today* **12** 853–859. (doi:10.1016/j.drudis.2007.08.006)

Semenza GL 2010 Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. *Oncogene* **29** 625–634. (doi:10.1038/onc.2009.441)

Semenza GL 2011 Oxygen sensing, homeostasis, and disease. *New England Journal of Medicine* **365** 537–547. (doi:10.1056/NEJMra1011165)

Semenza GL 2012 Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. *Trends in Pharmacological Sciences* **33** 207–214. (doi:10.1016/j.tips.2012.01.005)

Shah U, Giubellino A & Pacak K 2012 Pheochromocytoma: implications in tumorigenesis and the actual management. *Minerva Endocrinologica* **37** 141–156.

Singh RP, Franke K, Kalucka J, Mamlouk S, Muschter A, Gembarska A, Grinenko T, Willam C, Naumann R, Anastassiadis K *et al.* 2013 HIF prolyl hydroxylase 2 (PHD2) is a critical regulator of hematopoietic stem cell maintenance during steady-state and stress. *Blood* **121** 5158–5166. (doi:10.1182/blood-2012-12-471185)

Slane BG, Aykin-Burns N, Smith BJ, Kalen AL, Goswami PC, Domann FE & Spitz DR 2006 Mutation of succinate dehydrogenase subunit C results in increased $O_2\cdot -$, oxidative stress, and genomic instability. *Cancer Research* **66** 7615–7620. (doi:10.1158/0008-5472.CAN-06-0833)

Soga T 2013 Cancer metabolism: key players in metabolic reprogramming. *Cancer Science* **104** 275–281. (doi:10.1111/cas.12085)

Spitz DR 2011 Metabolic oxidative stress and low dose radiation responses: are mitochondria involved. *Health Physics* **100** 295. (doi:10.1097/HP.0b013e31820840aa)

Sun L, Bartlam M, Liu Y, Pang H & Rao Z 2005*a* Crystal structure of the pyridoxal-5′-phosphate-dependent serine dehydratase from human liver. *Protein Science* **14** 791–798. (doi:10.1110/ps.041179105)

Sun F, Huo X, Zhai Y, Wang A, Xu J, Su D, Bartlam M & Rao Z 2005*b* Crystal structure of mitochondrial respiratory membrane protein complex II. *Cell* **121** 1043–1057. (doi:10.1016/j.cell.2005.05.025)

Sutendra G & Michelakis ED 2013 Pyruvate dehydrogenase kinase as a novel therapeutic target in oncology. *Frontiers in Oncology* **3** 38. (doi:10.3389/fonc.2013.00038)

Sutendra G, Dromparis P, Kinnaird A, Stenson TH, Haromy A, Parker JM, McMurtry MS & Michelakis ED 2013 Mitochondrial activation by inhibition of PDKII suppresses HIF1a signaling and angiogenesis in cancer. *Oncogene* **32** 1638–1650. (doi:10.1038/onc.2012.198)

Taieb D, Sebag F, Barlier A, Tessonnier L, Palazzo FF, Morange I, Niccoli-Sire P, Fakhry N, De Micco C, Cammilleri S *et al.* 2009 ^{18}F-FDG avidity of pheochromocytomas and paragangliomas: a new molecular imaging signature? *Journal of Nuclear Medicine* **50** 711–717. (doi:10.2967/jnumed.108.060731)

Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, Frezza C, Bernard NJ, Kelly B, Foley NH *et al.* 2013 Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature* **496** 238–242. (doi:10.1038/nature11986)

Tennant DA & Gottlieb E 2010 HIF prolyl hydroxylase-3 mediates α-ketoglutarate-induced apoptosis and tumor suppression. *Journal of Molecular Medicine* **88** 839–849. (doi:10.1007/s00109-010-0627-0)

Tennant DA, Frezza C, MacKenzie ED, Nguyen QD, Zheng L, Selak MA, Roberts DL, Dive C, Watson DG, Aboagye EO *et al.* 2009 Reactivating HIF prolyl hydroxylases under hypoxia results in metabolic catastrophe and cell death. *Oncogene* **28** 4009–4021. (doi:10.1038/onc.2009.250)

Tian H, Hammer RE, Matsumoto AM, Russell DW & McKnight SL 1998 The hypoxia-responsive transcription factor EPAS1 is essential for catecholamine homeostasis and protection against heart failure during embryonic development. *Genes and Development* **12** 3320–3324. (doi:10.1101/gad.12.21.3320)

Timmers HJ, Kozupa A, Eisenhofer G, Raygada M, Adams KT, Solis D, Lenders JW & Pacak K 2007 Clinical presentations, biochemical phenotypes, and genotype–phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. *Journal of Clinical Endocrinology and Metabolism* **92** 779–786. (doi:10.1210/jc.2006-2315)

Timmers HJ, Gimenez-Roqueplo AP, Mannelli M & Pacak K 2009*a* Clinical aspects of SDHx-related pheochromocytoma and paraganglioma. *Endocrine-Related Cancer* **16** 391–400. (doi:10.1677/ERC-08-0284)

Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Havekes B, Eisenhofer G, Martiniova L, Adams KT & Pacak K 2009*b* Comparison of ^{18}F-fluoro-L-DOPA, ^{18}F-fluoro-deoxyglucose, and ^{18}F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. *Journal of Clinical Endocrinology and Metabolism* **94** 4757–4767. (doi:10.1210/jc.2009-1248)

Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Eisenhofer G, King KS, Rao JU, Wesley RA, Adams KT *et al.* 2012 Staging and functional characterization of pheochromocytoma and paraganglioma by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography. *Journal of the National Cancer Institute* **104** 700–708. (doi:10.1093/jnci/djs188)

Toledo RA, Qin Y, Srikantan S, Morales NP, Li Q, Deng Y, Kim SW, Pereira MA, Toledo SP, Su X *et al.* 2013 *In vivo* and *in vitro* oncogenic effects of HIF2A mutations in pheochromocytomas and paragangliomas. *Endocrine-Related Cancer* **20** 349–359. (doi:10.1530/ERC-13-0101)

Vegran F, Boidot R, Michiels C, Sonveaux P & Feron O 2011 Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-κB/IL-8 pathway that drives tumor angiogenesis. *Cancer Research* **71** 2550–2560. (doi:10.1158/0008-5472.CAN-10-2828)

Vicha A, Musil Z & Pacak K 2013 Genetics of pheochromocytoma and paraganglioma syndromes: new advances and future treatment options. *Current Opinion in Endocrinology, Diabetes, and Obesity* **20** 186–191. (doi:10.1097/MED.0b013e32835fcc45)

Viskochil D, Buchberg AM, Xu G, Cawthon RM, Stevens J, Wolff RK, Culver M, Carey JC, Copeland NG, Jenkins NA *et al.* 1990 Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* **62** 187–192. (doi:10.1016/0092-8674(90)90252-A)

Vogelstein B & Kinzler KW 2004 Cancer genes and the pathways they control. *Nature Medicine* **10** 789–799. (doi:10.1038/nm1087)

Walenta S & Mueller-Klieser WF 2004 Lactate: mirror and motor of tumor malignancy. *Seminars in Radiation Oncology* **14** 267–274. (doi:10.1016/j.semradonc.2004.04.004)

Warburg O 1956 On the origin of cancer cells. *Science* **123** 309–314. (doi:10.1126/science.123.3191.309)

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-13-0398

Published by Bioscientifica Ltd.

Warburg O, Wind F & Negelein E 1926 Über den Stoffwechsel der Tumoren in Körper. *Klinische Wochenschrift* **5** 829–832. (doi:10.1007/BF01726240)

Weber A, Hoffmann MM, Neumann HP & Erlic Z 2012 Somatic mutation analysis of the SDHB, SDHC, SDHD, and RET genes in the clinical assessment of sporadic and hereditary pheochromocytoma. *Hormones & Cancer* **3** 187–192. (doi:10.1007/s12672-012-0113-y)

Welsh SJ, Williams RR, Birmingham A, Newman DJ, Kirkpatrick DL & Powis G 2003 The thioredoxin redox inhibitors 1-methylpropyl 2-imidazolyl disulfide and pleurotin inhibit hypoxia-induced factor 1α and vascular endothelial growth factor formation. *Molecular Cancer Therapeutics* **2** 235–243.

Welsh S, Williams R, Kirkpatrick L, Paine-Murrieta G & Powis G 2004 Antitumor activity and pharmacodynamic properties of PX-478, an inhibitor of hypoxia-inducible factor-1α. *Molecular Cancer Therapeutics* **3** 233–244.

Xiao M, Yang H, Xu W, Ma S, Lin H, Zhu H, Liu L, Liu Y, Yang C, Xu Y *et al.* 2012 Inhibition of α-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors. *Genes and Development* **26** 1326–1338. (doi:10.1101/gad.191056.112)

Xie J, Wang BS, Yu DH, Lu Q, Ma J, Qi H, Fang C & Chen HZ 2011 Dichloroacetate shifts the metabolism from glycolysis to glucose oxidation and exhibits synergistic growth inhibition with cisplatin in HeLa cells. *International Journal of Oncology* **38** 409–417.

Yang C, Matro JC, Huntoon KM, Ye DY, Huynh TT, Fliedner SMJ, Breza J, Zhuang Z & Pacak K 2012 Missense mutations in human SDHB gene increase protein degradation without altering intrinsic enzymatic function. *FASEB Journal* **26** 4506–4516. (doi:10.1096/fj.12-210146)

Yankovskaya V, Horsefield R, Tornroth S, Luna-Chavez C, Miyoshi H, Leger C, Byrne B, Cecchini G & Iwata S 2003 Architecture of succinate dehydrogenase and reactive oxygen species generation. *Science* **299** 700–704. (doi:10.1126/science.1079605)

Yao L, Schiavi F, Cascon A, Qin Y, Inglada-Perez L, King EE, Toledo RA, Ercolino T, Rapizzi E, Ricketts CJ *et al.* 2010 Spectrum and prevalence of FP/TMEM127 gene mutations in pheochromocytomas and paragangliomas. *Journal of the American Medical Association* **304** 2611–2619. (doi:10.1001/jama.2010.1830)

Yeh IT, Lenci RE, Qin Y, Buddavarapu K, Ligon AH, Leteurtre E, Do Cao C, Cardot-Bauters C, Pigny P & Dahia PL 2008 A germline mutation of the KIF1Bβ gene on 1p36 in a family with neural and nonneural tumors. *Human Genetics* **124** 279–285. (doi:10.1007/s00439-008-0553-1)

Yu SJ, Yoon JH, Yang JI, Cho EJ, Kwak MS, Jang ES, Lee JH, Kim YJ, Lee HS & Kim CY 2012 Enhancement of hexokinase II inhibitor-induced apoptosis in hepatocellular carcinoma cells via augmenting ER stress and anti-angiogenesis by protein disulfide isomerase inhibition. *Journal of Bioenergetics and Biomembranes* **44** 101–115. (doi:10.1007/s10863-012-9416-5)

Yuneva M 2008 Finding an "Achilles' heel" of cancer: the role of glucose and glutamine metabolism in the survival of transformed cells. *Cell Cycle* **7** 2083–2089. (doi:10.4161/cc.7.14.6256)

Zelinka T, Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Reynolds JC, Ling A, Eisenhofer G, Lazurova I, Adams KT *et al.* 2008 Role of positron emission tomography and bone scintigraphy in the evaluation of bone involvement in metastatic pheochromocytoma and paraganglioma: specific implications for succinate dehydrogenase enzyme subunit B gene mutations. *Endocrine-Related Cancer* **15** 311–323. (doi:10.1677/ERC-07-0217)

Zhang C, Moore LM, Li X, Yung WK & Zhang W 2013 IDH1/2 mutations target a key hallmark of cancer by deregulating cellular metabolism in glioma. *Neurooncology* **15** 1114–1126. (doi:10.1093/neuonc/not087)

Zhuang Z, Yang C, Lorenzo F, Merino M, Fojo T, Kebebew E, Popovic V, Stratakis CA, Prchal JT & Pacak K 2012 Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. *New England Journal of Medicine* **367** 922–930. (doi:10.1056/NEJMoa1205119)

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