**REVIEW**

**HIF Signaling Pathway in Pheochromocytoma and Other Neuroendocrine Tumors**

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**Summary**

Hypoxia-inducible factors (HIFs) are transcription factors controlling energy, iron metabolism, erythropoiesis, and development. Dysregulation of these proteins contributes to tumorigenesis and cancer progression. Recent findings revealed the important role of HIFs in the pathogenesis of neuroendocrine tumors, especially pheochromocytoma (PHEO) and paraganglioma (PGL). PHEOs and PGLs are catecholamine-producing tumors arising from sympathetic- or parasympathetic-derived chromaffin tissue. To date, eighteen PHEO/PGL susceptibility genes have been identified. Based on the main signaling pathways, PHEOs/PGLs have been divided into two clusters, pseudohypoxic cluster 1 and cluster 2, rich in kinase receptor signaling and protein translation pathways. Recent data suggest that both clusters are interconnected via the HIF signaling and its role in tumorigenesis is supported by newly described somatic and germline mutations in HIF2A gene in patients with PHEOs/PGLs associated with polycythemia, and in some of them also with somatostatinoma. Moreover, HIFα signaling has also been shown to be upregulated in neuroendocrine tumors other than PHEO/PGL. Some of these tumors are components of hereditary tumor syndromes which can be associated with PHEO/PGL, but also in ileal carcinoids or melanoma. HIF signaling appears to be one of the crucial players in tumorigenesis, which could suggest new therapeutic approaches for treatment of neuroendocrine tumors.

**Key words**

Pheochromocytoma ● Paragangioma ● Hypoxia-inducible factor ● Oxygen sensing ● Therapy

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**Introduction**

PHEOs and PGLs are rare neuroendocrine catecholamine producing tumors. PHEOs arise from chromaffin cells within the adrenal medulla whereas tumors arising from extra-adrenal sympathetic and parasympathetic paraganglia are called PGLs (Pacak et al. 2007, Pacak 2011). The majority of PHEOs/PGLs are benign tumors but metastasis can also occur, especially in patients with a specific genetic background (Brouwers et al. 2006, Ayala-Ramirez et al. 2011, Eisenhofer et al. 2012). In the past, it was postulated that 10 % of these tumors were hereditary, but recent studies show 30-40 % PHEOs/PGLs to be genetically inherited (Neumann et al. 2002, Karasek et al. 2012). Moreover, 10-24 % of apparently sporadic tumors were found to have somatic mutations (Burnichon et al. 2011, Welander et al. 2012, Crona et al. 2014).

In this review, we focus on the role of hypoxia-
inducible factor signaling in neuroendocrine tumor development.

**Update on genetics of PHEO/PGL**

To date, 18 genes predisposing to PHEO/PGL development have been identified (Table 1). The susceptibility genes include the VHL tumor suppressor gene, the NF1 tumor suppressor gene, the RET proto-oncogene, the SDH complex subunits genes (SDHA, SDHB, SDHC, and SDHD), and the SDHAF2 gene (Karasek et al. 2012, Vicha et al. 2013). The new PHEO/PGL susceptibility genes include TMEM127, MAX, HIF2A and, by anecdotal reports, KIF1Bβ, PHD2/EGLN1, H-RAS, K-RAS, IDH, FH, and BAP1 genes (Hrascan et al. 2008, Ladroue et al. 2008, Schlisio et al. 2008, Gaal et al. 2010, Qin et al. 2010, Astuti et al. 2011, Comino-Mendez et al. 2011, 2013, Jiang and Dahia 2011, Wadt et al. 2012, Zhuang et al. 2012, Crona et al. 2013, Castro-Vega et al. 2014).

Two main clusters, based on the main signaling pathways, currently represent almost all hereditary PHEOs/PGLs: 1) cluster 1, a pseudohypoxic cluster, which is mainly represented by VHL, SDHx and, probably HIF2A and FH mutations, and 2) rich in kinase receptor signaling and protein translation pathways, cluster 2 is mainly composed of NF1, RET, KIF1Bβ, TMEM127, and MAX mutations (Dahia et al. 2005, Gimenez-Roqueplo et al. 2012, Vicha et al. 2013, Castro-Vega et al. 2014). Although cell signaling in these two clusters seems to be distinct, recent findings uniquely unify important existing connections between signaling pathways in both clusters. Not only that, the HIF signaling pathways appear to be a crucial, perhaps the most important player, in PHEO/PGL tumorigenesis.

**Table 1.** PHEO/PGL susceptibility genes and genotype-phenotype correlations.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Biochemical phenotype</th>
<th>Common PHEO/PGL sites</th>
<th>Malignant potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDHB</td>
<td>PGL4</td>
<td>1p36.13</td>
<td>AD</td>
<td>MN, NMN, MTY, NS</td>
<td>TAPGL/HNPGL/adrenal</td>
<td>43 %</td>
</tr>
<tr>
<td>SDHC</td>
<td>PGL3</td>
<td>1q21</td>
<td>AD</td>
<td>MN, NMN, NS</td>
<td>HNPGL/TAPGL/adrenal</td>
<td>Low</td>
</tr>
<tr>
<td>SDHD</td>
<td>PGL1</td>
<td>11q23</td>
<td>AD PI</td>
<td>MN, NMN, MTY, NS</td>
<td>HNPGL/TAPGL/adrenal</td>
<td>5 %</td>
</tr>
<tr>
<td>SDHAF2</td>
<td>PGL2</td>
<td>11q13.1</td>
<td>AD PI</td>
<td>Unknown</td>
<td>HNPGL</td>
<td>Unknown</td>
</tr>
<tr>
<td>VHL</td>
<td>VHL</td>
<td>3p25-26</td>
<td>AD</td>
<td>NMN</td>
<td>adrenal/TAPGL/HNPGL</td>
<td>Low (&lt;5 %)</td>
</tr>
<tr>
<td>NF1</td>
<td>NF1</td>
<td>17q11.2</td>
<td>AD</td>
<td>MN, NMN</td>
<td>Adrenal</td>
<td>11 %</td>
</tr>
<tr>
<td>RET</td>
<td>MEN</td>
<td>10q11.2</td>
<td>AD</td>
<td>MN, NMN</td>
<td>Adrenal</td>
<td>Low (&lt;1-5 %)</td>
</tr>
<tr>
<td>MAX</td>
<td></td>
<td>14q23.3</td>
<td>AD PI</td>
<td>MN and MN</td>
<td>Adrenal</td>
<td>10-25 %</td>
</tr>
<tr>
<td>TMEM127</td>
<td></td>
<td>2q11.2</td>
<td>AD</td>
<td>MN and MN</td>
<td>Adrenal/TAPGL/HNPGL</td>
<td>Rare (4 %)</td>
</tr>
<tr>
<td>HIF2A</td>
<td>Pacak-Zhuang</td>
<td>2p21-p16</td>
<td>Somatic</td>
<td>NMN</td>
<td>TAPGL/adrenal</td>
<td>Unknown</td>
</tr>
<tr>
<td>H-RAS</td>
<td>NA</td>
<td>11p15.5</td>
<td>Somatic</td>
<td>Unknown</td>
<td>Adrenal</td>
<td>Unknown</td>
</tr>
<tr>
<td>K-RAS</td>
<td>NA</td>
<td>12p12.1</td>
<td>Somatic</td>
<td>Unknown</td>
<td>Adrenal</td>
<td>Unknown</td>
</tr>
<tr>
<td>IDH1</td>
<td>NA</td>
<td>2q33.3</td>
<td>Somatic</td>
<td>Unknown</td>
<td>Unknown (HNPGL?)</td>
<td>Unknown</td>
</tr>
<tr>
<td>KIF1Bβ</td>
<td>NA</td>
<td>1p36.2</td>
<td>Somatic</td>
<td>Unknown</td>
<td>Unknown (Adrenal?)</td>
<td>Unknown</td>
</tr>
<tr>
<td>PHD2/EGLN1</td>
<td>1q42.1</td>
<td>Germline</td>
<td>Unknown</td>
<td>Unknown (TAPGL?)</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>FH</td>
<td>NA</td>
<td>1q43</td>
<td>Germline</td>
<td>Unknown</td>
<td>Adrenal/TAPGL</td>
<td>Unknown (potentially high)</td>
</tr>
<tr>
<td>BAP1</td>
<td>NA</td>
<td>3p21.1</td>
<td>Germline</td>
<td>Unknown</td>
<td>Unknown (TAPGL?)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Presenting only with PHEO/PGL together with polycythemia; most likely different from the typical somatic type of HIF2A mutation. AD, autosomal dominant; HNPGL, head and neck paraganglioma; MN, metanephrine; MTY, metoxytyramine; NMN, normetanephrine; NS, nonsecreting; PGL, paraganglioma; PHEO, pheochromocytoma; PI, paternal inheritance; TAPGL, thoracic or abdominal paraganglioma.
Hypoxia-inducible factors (HIFs)

HIFs are transcription factors which are activated under hypoxic or pseudohypoxic conditions and mediate adaptive responses of cells to these states, an idea originally pioneered by Semenza (2011) then later further studied and advanced by others (Schofield and Ratcliffe 2004, Kaelin and Ratcliffe 2008). Hypoxia reflects the lack of sufficient oxygen supply (O2 concentration drops below 21 %); pseudohypoxia is the state where oxygen is present in a sufficient amount in cells but cannot be processed and further utilized due to an alteration in oxygen-sensing pathways. HIFs are composed of stable, constitutively expressed β-subunit, and ubiquitously expressed, oxygen-sensitive α-subunits, consisting of three isoforms; HIF-1α, HIF-2α, and HIF-3α (Schofield and Ratcliffe 2004, Kaelin and Ratcliffe 2008, Keith et al. 2012).

Under normoxic conditions, HIF-1α and HIF-2α are degraded via the ubiquitin-proteasome pathway, which is controlled by several key enzymatic reactions, the first including prolyl hydroxylation by PHDs (also called as the main O2 sensors) and the second represented by subsequent bindings to the VHL protein (for a review, see Kaelin and Ratcliffe 2008, Koh and Powis 2012). When these enzymatic reactions occur, HIFs do not stabilize well and they are degraded quickly by the proteasome. Additional and less important negative regulation of HIF is mediated via the HIF-3α2 splice variant (IPAS), which forms inactive complexes with HIF-1α, and also via the FIH1 that hydroxylases HIF on the asparaginyl residue of the C-terminal domain. FIH1 blocks HIF-1α interaction using coactivators with proteasome ultimately breaking down the complex (Makino et al. 2001, Lando et al. 2002, Jang et al. 2005, Heikkila et al. 2011).

Hypoxia or pseudohypoxia lead to HIFα stabilization and its heterodimerization with HIF-β, binding of coactivators, and the transactivation of HIF target genes, including those associated with angiogenesis, hematopoeisis, glycolysis, cell growth, and cell migration (Maxwell et al. 2001, Lau et al. 2007, Kaelin and Ratcliffe 2008).

HIF-1α and HIF-2α are the best studied isoforms and were found to have mostly complementary, but also opposite functions (Hu et al. 2003, Carroll and Ashcroft 2006, Rankin et al. 2007). HIF-1α is activated during short periods of severe hypoxia, while HIF-2α is active under mild hypoxia for more prolonged periods of time (Holmquist-Mengelbier et al. 2006). Term mild hypoxia is used for oxygen concentrations in tissues of 1-5 % and severe hypoxia is defined as below 1 % (Koh and Powis 2012). The distinct effect of different oxygen concentrations on HIFα activation is mediated by HAF, which marks HIF-1α for degradation but transactivates HIF-2α by binding to a different protein site than in HIF-1α (Koh et al. 2008, 2011). Moreover, both HIF-1α and HIF-2α functionally interact with many other signal transduction and transcriptional systems, including NOTCH, WNT, and MYC pathway; thus, HIFs can also regulate gene expression via a hypoxia-independent mechanism (Kaelin and Ratcliffe 2008).

Distinct regulation of HIFα isoforms leads to distinct expression patterns of these transcription factors. HIF-1α is expressed in all cells, whereas HIF-2α is preferentially expressed in the endothelium, kidney, heart, lung, gastrointestinal epithelium, and neural crest cell derivatives, including chromaffin cells (Wiesener et al. 2003, Keith et al. 2012). HIF-2α was shown to play an important role in the regulation of developmental processes of sympathoadrenal lineage; it also regulates catecholamine synthesis and secretion reflected by a typical noradrenergic phenotype (for a review, see Richter et al. 2013).

HIF signaling in tumorigenesis

HIF interaction with many signaling and transduction pathways and the presence of (pseudo)hypoxia in cancer lead to the presumption that HIF is one of the most important players in tumorigenesis. It was found that both HIF-1α and HIF-2α are overexpressed in most human cancers (Zhong et al. 1999, Talks et al. 2000, Hockel and Vaupel 2001). HIF-1α and HIF-2α expression in tumors vary among cell types and these differences most probably reflect the consequences of preferential HIF-1α or HIF-2α function in different cancer cell subtypes, varying stages of tumor progression (including a degree of hypoxia), and within microenvironmental changes of the tumor (Blouw et al. 2003, Raval et al. 2005, Semenza 2010, Keith et al. 2012). Although both HIFα subunits are often overexpressed in many tumors, HIF-2α is preferentially linked to more aggressive lesions with a higher metastatic potential or already present metastases (Warnecke et al. 2004, Koh and Powis 2012).

Thus, HIF-2α overexpression was found to be associated with metastatic progression and poor
prognosis in specific cancer types, especially astrocytoma, glioma, neuroblastoma, head and neck cancers, and melanoma (Keith et al. 2012). In renal cell carcinoma, in which VHL mutations lead to decreased HIFα degradation by the defective bindings of hydroxylated HIFs to pVHL, HIF-2α stabilization leads to the tumor formation in mice (Kondo et al. 2003) and protumorigenic genes were shown to be more HIF-2α dependent (Raval et al. 2005). However, it was also shown that both HIF-2α upregulation and downregulation can promote tumor development and progression (Kim et al. 2009, Mazumdar et al. 2010) therefore, a certain balance between HIF-1α and HIF-2α is needed for optimal function, specifically in tumors. Moreover, HIF-2α has been shown to regulate HIF-1α target genes expression in the absence of HIF-1α and vice versa (Keith et al. 2012, Koh and Powis 2012). Thus, it is not surprising that renal cell carcinomas may be divided into two major subgroups; those preferentially expressing HIF-1α and those with combined expression of HIF-1α and HIF-2α.

HIF activation in cancer is mediated not only via the (pseudo)hypoxia signaling pathway but also via multiple oxygen-independent oncogenic pathways, including growth factor signaling pathways and a loss of tumor suppressor genes (for a review, see Jochmanova et al. 2013, Richter et al. 2013).

HIF in PHEO/PGL development

The role of HIF in the PHEO/PGL pathogenesis has been anticipated for a long time since HIF pathway was previously found to be dysfunctional in these tumors (Maxwell et al. 2001, Dahia et al. 2005, Favier and Gimenez-Roqueplo 2010). Interestingly, most of hereditary PHEOs/PGLs are indeed related to the hypoxia signaling pathway, mainly through the mutations within the \textit{VHL, PHD2, FH, SDHx}, and \textit{SDHAF2} genes (Jafri and Maher 2012, Toledo et al. 2013, Castro-Vega et al. 2014), which lead to increased stability of HIF (Gimenez-Roqueplo et al. 2001). In the RET- and \textit{NF1}-associated PHEOs/PGLs, the activation of the RAS-MAPK-mTORC pathway is present, which leads to HIF-1α activation (Eisenhofer et al. 2004a, Dahia et al. 2005, Johannessen et al. 2005, Foster and Fingar 2010, Lopez-Jimenez et al. 2010). In tumors associated with \textit{TMEM127} and \textit{MAX} mutations, HIFα levels seem to be increased also due to mTORC activation (Brugarolas et al. 2004, Land and Tee 2007; for a review, see Jochmanova et al. 2013). \textit{K-RAS} and recently described \textit{H-RAS} mutations in PHEOs/PGLs lead to the activation of the RAS/RAF/ERK pathway, a part of the RAS/MAPK pathway (Hrascan et al. 2008, Crona et al. 2013), and to the increased HIFα signaling. \textit{FH} mutations result in a loss of fumarate hydratase activity, an enzyme important in the Krebs cycle. \textit{FH}-related PHEOs/PGLs had widespread alterations in protein succination and displayed the same epigenetic changes as \textit{SDHB}-related tumors (Castro-Vega et al. 2014).

One of the most recently described genes associated with PHEO/PGL development is \textit{HIF2A}. Initially, somatic gain-of-function \textit{HIF2A} mutations were found in tumors from two female patients with multiple PGLs and polycythemia. One of these patients also presented with somatostatinoma (Zhuang et al. 2012). Subsequently, two other patients with multiple PGLs and somatostatinomas associated with polycythemia were also found to have somatic \textit{HIF2A} mutations, suggesting the existence of a new syndrome described by Pacak and Zhuang (Pacak et al. 2013). \textit{HIF2A} mutations result in HIF-2α protein stabilization by affecting its hydroxylation, which prevents recognition of HIF-2α by VHL and results in increased HIF-2α protein half-life followed by changes in transcriptional activity of many hypoxia-related genes (Zhuang et al. 2012, Yang et al. 2013). Further investigations revealed other patients with PHEO and this syndrome, extending the clinical characteristics of the Pacak-Zhuang syndrome to multiple PHEOs (Taieb et al. 2013). Subsequently, Lorenzo et al. (2013) found a male patient presenting with PHEO and PGLs associated with polycythemia due to a germline \textit{HIF2A} mutation and Favier et al. (2012) identified a \textit{HIF2A} mutation in PHEO resected from a 24-year-old female without polycythemia. However, none of these presented with somatostatinoma. Comino-Méndez et al. (2013) described three additional female patients with multiple PHEOs/PGLs and polycythemia and three patients with apparently sporadic disease. The other patient with somatic \textit{HIF2A} mutation – female presenting with polycythemia, PHEO, PGLs and somatostatinoma – has been described recently by Buffet et al. (2014). They also found a \textit{HIF2A} heterozygous mutation in a male patient with polycythemia and PGL; the mutation was present in the PGL tissue but also as a mosaic in leukocyte DNA and DNA extracted from buccal cells. HIF-2α stabilization and its involvement in the pathogenesis of PHEOs/PGLs is also supported by the presence of only the noradrenergic biochemical
phenotype, which reflects the involvement of HIF-2α in preferential norepinephrine synthesis as described previously (Tian et al. 1998, Eisenhofer et al. 2004b, Nilsson et al. 2005). In summary, the presence of multiple PHEOs/PGLs and duodenal somatostatinomas associated with polycythemia currently seem to only be present in female patients.

Previously, dominantly inherited gain-of-function HIF2A mutations were found to be associated with congenital polycythemia (Percy et al. 2008, Prchal and Gordeuk 2008), which stresses the role of HIF-2α in the regulation of erythropoiesis. HIF-2α stabilization and PGL-associated erythropoietin production have been also found in patients with PHD2 and VHL mutations (Ladroue et al. 2008, Capodimonti et al. 2012).

The role of HIF in PHEO/PGL pathogenesis is further supported by the gene expression profiling study, which revealed distinct differences in gene expression between both hereditary and sporadic norepinephrine- and epinephrine-producing PHEOs/PGLs including detection of genes involved in hypoxia-angiogenic pathways, especially HIF2A (Eisenhofer et al. 2004b). Later on, in the study of Dahia et al. (2005), cluster 1 tumors were found to display a gene signature of the activated hypoxia pathway, associated with enhanced angiogenesis and extracellular matrix processes, which are known to be HIF-1α signaling dependent. Subsequent other gene expression profiling studies confirmed strong HIF2A expression in VHL and SDHx tumors (Lopez-Jimenez et al. 2010, Burnichon et al. 2011). Moreover, Lee et al. (2005) proposed that the PHEO/PGL mutations of NF1, RET, VHL and SDHx all act on the same signaling network, resulting in decreased apoptosis (also dependent on the HIF signaling pathway) during chromaffin cell development and tumor formation; additionally, cluster 2 gene mutations seem to enhance HIF-2α signaling in cells (for a review, see Jochmanova et al. 2013, Richter et al. 2013).

**HIF and other neuroendocrine tumors**

The HIFα signaling has also been shown to be upregulated in neuroendocrine tumors other than PHEO/PGL. Some of these tumors are components of hereditary tumor syndromes which can be associated with PHEO/PGL, e.g. VHL disease caused by the mutation of VHL or MEN due to the mutations in the RET proto-oncogene. In MEN type 1, pituitary, parathyroid and pancreas tumors are present, while in MEN type 2, there are medullary thyroid carcinomas, PHEO, and parathyroid tumors or, simply with mucosal neuromas (Gaztambide et al. 2013, Lodish 2013). Medullary thyroid cancer is rare and typically occurs as a part of MEN2. A recent study by Takacova et al. (2014) brought the experimental evidence for the crosstalk between RET and HIF-1.

Speksy et al. (2012) studied the expression of 52 genes in patients with VHL and sporadic pancreatic neuroendocrine tumors. They found upregulation of genes directly related to HIF signaling (CA9, HIF2A, GLUT1), angiogenesis, epithelial to mesenchymal transition, and metastasis in VHL pancreatic neuroendocrine tumors.

Tumor hypoxia and overexpression of HIF-1α and HIF-2α were also found in ileal carcinoids. HIF-2α expression was significantly higher in distant metastasis compared to a primary tumor in the same patient. Immunohistochemical analysis demonstrated expression of VEGF and CA9. Expression profiling of hypoxic carcinoid cells revealed significant regulation of a large number of genes, including the chemokine receptor CXCR4 (Arvidsson et al. 2010).

It has also been demonstrated that hypoxia can induce NOTCH downstream signaling in several tumor cell lines. Accumulation of HIF-2α promotes an aggressive phenotype with dedifferentiation and activation of NOTCH signaling in neuroblastoma cells (Jogi et al. 2004, Holmquist-Mengelbier et al. 2006, Sahlgren et al. 2008).

High expression levels of HIF-1α, HIF-2α and their target genes have been detected in melanoma cells and they were found to be related to a poor prognosis of patients (Zhong et al. 1999, Giatromanolaki et al. 2003, Valencak et al. 2009). Enhanced expression of HIFs, transcription of their target genes, and altered metabolism in melanoma cells during disease progression may promote malignant reprogramming and acquisition of stem cell-like properties and more aggressive and metastatic phenotypes, reviewed by Mimeault and Batra (2013).

**Conclusions and future treatment options**

HIFα signaling appears to be a central signaling pathway involved in the pathogenesis of hereditary PHEOs/PGLs, sporadic PHEOs/PGLs, and other neuroendocrine tumors. This designates HIFα as a very promising therapeutic target, especially for more
aggressive and metastatic tumors where the introduction of HIF-2α is of the greatest interest at present. Nowadays, several agents affecting HIF-1α signaling have been introduced, with various results depending on a cancer HIFα phenotype (Liu et al. 2014, for a review, see Melillo 2007a,b). Nevertheless, drugs selectively targeting the HIF-2α signaling pathways have not yet been described but are currently under development (Rogers et al. 2013, Scheuermann et al. 2013). Moreover, it has been shown that HIF-1α and HIF-2α can activate different genes (Keith et al. 2012, for a review, see Koh and Powi 2012); therefore, the development of drugs targeting both HIF-1α and HIF-2α is of great interest. It was shown that HAF switches cells from HIF-1α to HIF-2α signaling; in light of that, one therapeutic approach could be to change the balance of HIFα isoforms by modulating HAF signaling in tumors (Koh et al. 2011). Further investigations are needed to elucidate the other signaling pathways involved in PHEO/PGL development and crosstalk within these pathways and HIF signaling pathway. The combination of two or three drugs, one of them targeting the HIFα signaling pathway and the other two regulating signaling pathways independently of HIFs, could potentially serve as a promising therapeutic strategy in combatting metastatic neuroendocrine tumors, especially PHEO/PGL.

Finding of novel diagnostic tests based on biomarkers (detected either biochemically or by molecular imaging) associated with hypoxia and altered metabolic pathways (by measurement of various metabolites, specifically within the Krebs cycle) should also help to select patients who are likely to respond to that specific type of therapy (e.g. to the HIF signaling inhibitors) and to personalize anti-cancer treatment. We predict that the introduction of novel HIF-related therapies will soon be integrated into medical practices that are specialized in the treatment of neuroendocrine tumors.

Conflict of Interest
There is no conflict of interest.

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Abbreviations
BAP1, BRCA1-associated protein-1; CA9, carbonic anhydrase-IX; CXCR4, C-X-C chemokine receptor type 4; ERK, extracellular signal-regulated kinase; FH, fumarate hydratase; FIH1, factor inhibiting HIF; GLUT1, glucose transporter 1; HAF, hypoxia-associated factor; HIF, hypoxia-inducible factor; HIF2A, hypoxia-inducible factor 2-alpha gene; H-RAS, Harvey rat sarcoma viral oncogene; IPAS, inhibitory PAS domain protein; IDH, isocitrate dehydrogenase; KIF1Bβ, kinesin family member 1B, transcript variant β; K-RAS, Kirsten rat sarcoma viral oncogene; MAPK, mitogen activated protein kinases; MAX, MYC-associated factor X; MEN, multiple endocrine neoplasia; mTORC, mammalian target of rapamycin complex; MYC, v-myc avian myelocytomatosis viral oncogene homolog; NF1, neurofibromatosis type 1; PGL, paraganglioma; PHD, prolyl hydroxylase; PHD2/EGLN1, prolyl hydroxylase 2; PHEO, pheochromocytoma; pVHL, von Hippel-Lindau protein; RAF, proto-oncogene serine/threonine-protein kinase; RET, rearranged during transfection; SDH, succinate dehydrogenase; SDHAF2, SDH complex assembly factor 2; TMEM127, transmembrane protein 127; VEGF, vascular endothelial growth factor; VHL, von Hippel-Lindau.

References


