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Current Perspective

HIF-2alpha: Achilles' heel of pseudohypoxic subtype paraganglioma and other related conditions

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Abstract Paragangliomas (PGLs) belong to the most hereditary endocrine tumours. The existence of mutated HIF2A in these tumours, the role of oncometabolites on HIFs stabilisation and a recent concept proposing how hereditary PGLs converge on the hypoxia-signalling pathway, brought solid evidence of the existence of PGL hypoxiom. Hypoxia-inducible factor 2alpha (HIF-2α) antagonists -PT2385, and PT2399 have been shown to have promising results in the management of clear cell renal cell carcinoma by targeting the HIF-2α pathway in recent and ongoing clinical trials (PT2799). The main aim of this perspective is to address the possibility of HIF-2α antagonists in the management of tumours, beyond clear cell renal cell carcinoma, where the dysfunctional hypoxia-signalling pathway, especially HIF-2α, referred here as the Achilles' heel, plays a unique role in tumorigenesis and other disorders. These tumours or disorders include PGLs, somatostatinomas, hemangioblastomas, gastrointestinal stromal tumours, pituitary tumours, leiomyomas/leiomyosarcomas, polycythaemia and retinal abnormalities. We hope that HIF-2α antagonists are likely to emerge as a potential effective treatment of choice for HIF-2α–related tumours and disorders.

Abbreviations: SDHx, Succinate dehydrogenase complex; *FH*, Fumarate hydratase; *MDH2*, Malate dehydrogenase 2; *VHL*, Von Hippel-Lindau; *HIF2A*, Hypoxia-inducible factor 2 alpha; *PHD1*, Prolyl hydroxylase 1; *PHD2*, Prolyl hydroxylase 2; *DNA*, Deoxyribonucleic acid; *ARNT*, Aryl hydrocarbon receptor nuclear translocator; *VEGFA*, Vascular endothelial growth factor A; *GLUT1*, Glucose transporter 1; *PAI-1*, Plasminogen activator inhibitor-1; *CCND1*, Cyclin D1; *Scgb3a1*, Secretoglobin Family 3A Member 1.

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Paragangliomas (PGLs) are neuroendocrine neoplasms arising from neural crest tissues and belong to the most hereditary endocrine tumours with 27% having known, PGL susceptibility gene [1]. The pioneering work of Dahia *et al.* [2] underlying the importance of hypoxia-inducible factors (HIFs) in PGL pathogenesis, the existence of mutated *HIF2A* in these tumours [3], oncometabolites role on HIFs stabilisation, and a recent concept proposing how hereditary PGLs converge on the hypoxia-signalling pathway [4], brought solid evidence of the existence of PGL hypoxiom.

1. HIF-2α: The Achilles' heel

Krebs cycle (*SDHx*, *FH*, *MDH2*) and hypoxia-signalling pathway (*VHL*, *HIF2A*, *PHD1*, *PHD2*) PGL-related genes (Fig. 1), all belonging to Cluster 1 PGLs, function as poisoned arrows that hit Achilles' heel and HIFs, promoting chromaffin/paraganglionic cell tumorigenesis. For example, *SDHx* and *FH* mutations result in the accumulation of either succinate or fumarate, both acting as oncometabolites. Oncometabolites act as competitive inhibitors of PHDs, causing a 'pseudohypoxic' environment leading to HIFs stabilisation. These oncometabolites also cause DNA hypermethylation, leading to epigenetic silencing of genes involved in catecholaminergic cell differentiation, promoting PGL formation. In contrast, mutations in hypoxia-signalling pathway genes related to PGL development lead to direct HIFs stabilisation, preferentially HIF-2α [4]. In a pseudohypoxic subtype of PGL, *VHL* mutations prevent degradation of HIF, causing unregulated angiogenesis and tumour formation [4]. Zhuang *et al.* [3] reported mutations occurring close to HIF-2α hydroxylation site that resulted in decreased HIF-2α prolyl hydroxylation, decreased VHL binding to HIF-2α, and its stabilisation resulting in PGLs, somatostatinomas, and polycythaemia. In chronic hypoxic conditions, hypoxia-activating factor switches the transcription of HIF-1α to HIF-2α, which plays an important role in tumour adaptation and proliferation. Due to this switch, HIF-2α expression increases leading to tumour progression.

2. Targeting the Achilles' heel by HIF-2α antagonists

Recently, HIF-2α antagonists have become drugs of interest in treating tumours where dysfunctional hypoxia-signalling pathway seems to play an important role in tumorigenesis; particularly in clear cell renal cell carcinoma (ccRCC) that is characterised by the inactivation of *VHL*, *FH*, and *SDHx* as seen in pseudohypoxic subtypes of PGL. In recent studies [5,6], in VHL-mutated ccRCC, the HIF-2α antagonist, PT2399, decreased the dimerisation of HIF-2α with HIF-1β subunit, thereby inhibiting the transcription of HIF-2α target genes (e.g. *VEGFA*, *GLUT1*, *PAI-1*, or *CCND1*) leading to the suppression of tumour growth. Moreover, PT2385 also resulted in decreased erythropoietin, making it a promising drug in *HIF2A mutation-related* polycythaemia and PGLs. The other HIF-2α antagonist, PT2977, is currently being evaluated in a phase 1 study against solid tumours and ccRCC (NCT02974738).

The use of HIF-2α antagonists may be also beneficial in other HIF-2α–related conditions such as somatostatinoma and retinal abnormalities caused by *HIF2A* mutations; polycythaemia in *HIF2A* and *PHDs* mutations; RCC, central nervous system and retinal haemangioblastomas, pancreatic endocrine tumours in VHL syndrome; and finally, RCC, uterine and cutaneous leiomyomas/leiomyosarcomas in *FH* mutations. Though HIF-2α antagonists opened a new door in management of these cancers, development of other drugs that act on the HIF pathway are still in infancy and more work is clearly needed. However, with the increasing evidence of divergent and opposing functions of HIF-1α and HIF-2α on various genes including p53 and the differential regulation of HIF-1α and HIF-2α post-translationally [7], one must be cautious about HIF-2α inhibitors treatment efficacy in various cancers. For example, as seen in KRAS-driven mouse models of lung cancer, HIF-2α suppression inhibited tumour growth or sometimes promoted tumour growth in the same tumour context by inhibiting the tumour suppressor *Scgb3a1*, a HIF-2α target gene. This suggests that the effective targeting of HIF-α subunits in cancer management is challenging, sometimes causing opposing results.

3. Future directions

Promising outcomes of PT2399 described in the management of pseudohypoxic ccRCCs, opened a new insight of treating the above mentioned lethal cancers by targeting HIF-2α. We expect that HIF-2α antagonists could well offer effective targeted therapy for patients; particularly with pseudohypoxic metastatic PGLs and could improve their clinical outcome. Since these pseudohypoxic PGLs can exhibit accelerated glycolysis (Warburg effect), and glutaminolysis, the concept of multi-targets therapeutic approach including HIF-2α antagonist could become more beneficial. The other potential treatment options in these tumours are prolyl hydroxylase activators (R59949 and KRH102053) that promote hydroxylation of HIF making it vulnerable for degradation by VHL thereby causing anti-tumour effect. HIF-2α translational inhibitors could be the other classes of drugs to have a potential to increase the HIF-2α degradation. Histone deacetylase inhibitors are also an option in the management of these tumours as transcription repressors of HIF and VEGF by blocking the acetylation of histone and causing chromatin condensation. Thus, long-awaiting high-throughput