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Gene Section
Review

EPAS1 (Endothelial PAS Domain Protein 1)

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Abstract

Review on EPAS1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ECYT4, HIF2A, HLF, MOP2, PASD2, bHLHe73

HGNC (Hugo): EPAS1

Location: 2p21

Local order: RPL26P15 - RPL36AP14 - uncharacterized LOC101926974 - **EPAS1** - uncharacterized LOC101805491 - TMEM247 - ATP6V1E2.

DNA/RNA

Description

Genomic size: Starts at 46524541 and ends at 46613842.

Transcription

Transcript length: The gene is comprised of 16 exons, constituting one main transcript of 5184 base pairs.

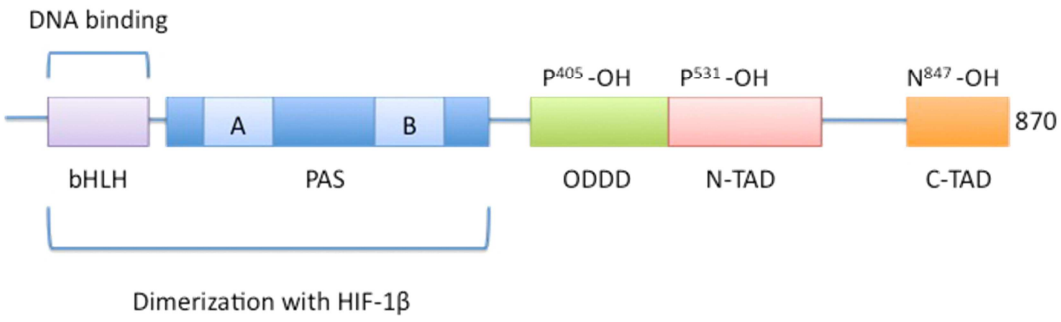
Pseudogene

None described.

Protein

Description

The HIF-2α protein is 870 amino acids long and consists of a basic-helix-loop-helix domain, two PER-ARNT-SIM domains (A and B), an oxygen-dependent degradation domain (ODDD) and two transcriptional-activation domains (N-TAD and C-TAD). Two proline residues (P^{405} in ODDD and P^{531} in N-TAD) and an asparaginyl residue (N^{847} in C-TAD) are subjected to hydroxylation during physiologic oxygen tensions, regulating the stability and activity of the HIF-2α protein.



Representation of the EPAS1/HIF2A protein with its specific domains specified. Critical hydroxylation sites are indicated.

Phosphorylation of HIF-2α at T^{844} has been reported as necessary for its transcriptional activation function (Gradin et al., 2002).

Expression

In adult human tissue, HIF-2α protein is mainly expressed in cells experiencing low oxygen levels, and the HIF-2α mRNA has been shown to be predominantly expressed in highly vascularized tissues (Tian et al., 1997). During human embryonic and fetal development, HIF-2α is transiently but specifically expressed in cells of the developing sympathetic nervous system (SNS) (Nilsson et al., 2005; Mohlin et al., 2013). In embryonic and adult mouse tissue, the expression of HIF-2α mRNA is more or less restricted to endothelial cells (Tian et al., 1997; Jain et al., 1998). In a zebrafish model, the HIF-2α transcript is expressed early in brain tissue and blood vessels, and later on HIF-2α replaces HIF-1α transcription in the notochord (Rojas et al., 2007).

Localisation

HIF-2α is part of a transcriptional complex and is hence localized mainly in the nucleus upon hypoxic induction. However, HIF-2α protein can also be detected in the cytoplasm, at hypoxic conditions and foremost at more physiological oxygen conditions, as demonstrated in cultured cells in vitro and in tumor specimens in vivo (Holmquist-Mengelbier et al., 2006). These findings were recently strengthened by the demonstration of a role for HIF-2α as part of an oxygen-regulated translation initiation complex and presence of HIF-2α in the cellular polysome fraction (Uniacke et al., 2012).

Function

At lower oxygen tensions, the hydroxylation of HIF-2α by prolyl hydroxylases (PHDs) and Factor Inhibiting HIF (FIH) is prevented, and the HIF-2α subunit relocates to the nucleus where it forms a transcriptional complex together with its binding partner ARNT (also known as HIF-1β) and co-factors such as p300 and CBP. By binding to hypoxia response elements (HREs) in the promoter of target genes, the HIF complex initiates transcription of numerous genes involved in a variety of tumorigenic cellular processes, including angiogenesis, invasion and metastasis, growth, dedifferentiation, and apoptosis (Semenza, 2003). As mentioned under the Localization section, HIF-2α has also been demonstrated to be part of a hypoxia-regulated translation initiation complex. Hypoxia induces HIF-2α to form a complex together with RNA-binding protein RBM4 and cap-binding eIF4E2, and this complex is then recruited to a wide variety of mRNAs, promoting active translation at polysomes (Uniacke et al., 2012). In a recent report, HIF-2α was further shown to protect human hematopoietic stem/progenitor cells from endoplasmic reticulum (ER) stress-induced apoptosis and to enhance the long-term repopulating ability of these cells (Rouault-Pierre et al., 2013).

Homology

HIF-2α is part of the basic helix-loop-helix-PAS family of proteins and is structurally related to the HIF-1α and HIF-3α subunits. While HIF-3α is believed to negatively regulate the other two alpha subunits (Makino et al., 2001; Maynard et al., 2007), HIF-1α and HIF-2α share both sequence similarity and target genes. However, despite 48% primary amino acid sequence homology between HIF-1α and HIF-2α (Tian et al., 1997), it is becoming increasingly evident that these two proteins also function at distinct sites and during differential cellular conditions.

Mutations

Germinal

Functional mutations in human EPAS1 are associated with variations in hemoglobin and red blood cell concentration (Percy et al., 2008b; Beall et al., 2010; Yi et al., 2010). Percy et al. described a gain of function mutation in a family with high hemoglobin concentrations and erythrocytosis (Percy et al., 2008b). Similar mutations, all associated with small amino acid substitutions leading to protein stabilization, have been reported in other clinical cases (Gale et al., 2008; Martini et al., 2008; Percy et al., 2008a; van Wijk et al., 2010). In contrast, EPAS1 mutations associated with a loss of function and low hemoglobin concentrations have been described in healthy individuals living at high altitudes. Extensive analysis of genome-wide sequence variations and exome sequencing in Tibetans have shown that EPAS1 is a key gene mutated in Tibetan populations (Beall et al., 2010; Simonson et al., 2010; Yi et al., 2010; Peng et al., 2011). The functional consequence of EPAS1 SNPs associated with low hemoglobin concentrations is described as adaptation to low oxygen without elevated red blood cell production, thereby avoiding high blood viscosity creating cardiovascular risks.

Somatic

Several studies have recently identified the first mutations in any of the HIF alpha subunits in cancer. Somatic gain-of-function mutations in exon 12 of the EPAS1 gene in two patients with paraganglioma and associated erythrocytosis results in an amino acid substitution in proximity to the PHD hydroxylation site and increased protein half-life and HIF-2α activity (Zhuang et al., 2012).

Additional mutations in EPAS1 have also been identified in patients with paraganglioma and pheochromocytoma without associated erythrocytosis (Comino-Mendez et al., 2013), and in patients with somatostatinoma and paraganglioma (Yang et al., 2013).

Implicated in

Renal clear cell carcinoma

Note

The predominant loss of von Hippel Lindau in clear cell renal cell carcinoma (ccRCC), results in defective targeting of HIF-α proteins for degradation at normoxia (Gnarra et al., 1994). Therefore, both HIF-1α and HIF-2α accumulate irrespective of oxygen levels in VHL-defective cells and are abundantly expressed in cells of ccRCC origin (Krieg et al., 2000).

For unknown reasons, the expression of HIF-2α is more prominent than that of HIF-1α in RCC cell lines and tumors and HIF-1α expression is often lost in RCC cell lines (Maxwell et al., 1999; Krieg et al., 2000).

Regulation of HIF target genes in RCC cell lines are more dependent on HIF-2α than on HIF-1α and silencing of HIF-2α in VHL-deficient cells suppress tumor growth, suggesting an important role for HIF-2α in renal carcinoma (Kondo et al., 2003; Carroll et al., 2006).

Paraganglioma/pheochromocytoma

Note

Paraganglioma and pheochromocytoma derive from the chromaffin cell lineage of the sympathetic nervous system, and notably, genes involved in the hypoxic response (e.g. VHL and SDH genes) are frequently mutated in these tumors (Neumann et al., 2002). Recently, somatic mutations in the EPAS1 gene itself were discovered in two paraganglioma patients, describing the first cases of EPAS1 mutations in any cancer type (Zhuang et al., 2012). These gain-of-function mutations lead to increased protein half-life and HIF-2α activity, in turn resulting in up-regulation of HIF-2α downstream target genes, presumably explaining the clinical presentation in these patients. In a follow-up study, two additional EPAS1 mutations were discovered in patients presenting with polycythemia and somatostatinoma or paraganglioma (Yang et al., 2013). These novel mutations lead to disruption of the ODD domain-PHD2 interaction and thereby result in less ubiquitination and higher activity of the HIF-2α protein. In another study, 7 out of 41 examined patients with pheochromocytoma or paraganglioma presented with somatic EPAS1 mutations, and interestingly, three of these cases were also accompanied by an exclusive gain of chromosome 2p (Comino-Mendez et al., 2013).

Neuroblastoma

Note

In the childhood tumor neuroblastoma, HIF-2α positive tumor cells have been identified in a perivascular niche, suggesting a non-hypoxic driven expression (Pietras et al., 2008). The HIF-2α positive cells display an immature tumor stem cell-like phenotype and their presence in neuroblastoma specimens correlate to poor overall survival (Holmquist-Mengelbier et al., 2006; Noguera et al., 2009). In neuroblastoma cell lines, HIF-2α is expressed at hypoxic conditions (1% oxygen) and at near end-capillary physiological oxygen levels (5% oxygen) (Jogi et al., 2002; Holmquist-Mengelbier et al., 2006). At prolonged hypoxic conditions, HIF-2α is continuously expressed in contrast to its homologue HIF-1α. In addition, overexpression of HIF-2α in a mouse neuroblastoma cell line promoted in vivo tumor angiogenesis, while mutant HIF-2α cells formed tumors that were highly necrotic (Favier et al., 2007).

Glioma

Note

Knockdown of HIF-2α expression can reduce vascularization but accelerate tumor growth of human glioblastoma cells pointing to a role for HIF-2α as a tumor suppressor in glioblastoma (Acker et al., 2005). In contrast, recent work has focused on HIF-2α as a putative glioblastoma cancer stem cell (CSC) marker. Specifically, HIF-2α protein expression co-localizes with CD133 in a fraction of tumor cells (McCord et al., 2009) and with cancer stem cell markers in glioma specimens (Li et al., 2009). Glioblastoma putative CSCs respond to hypoxia by induction of HIF2-α (Li et al., 2009; Seidel et al., 2010), and inhibiting HIF2-α in glioblastoma CSCs decreases self-renewal, proliferation and survival in vitro and tumor-initiating capacity in vivo (Li et al., 2009). In addition, elevated HIF2A mRNA levels are associated with poor prognosis in glioma patients (Li et al., 2009).

Breast cancer

Note

HIF-2α is expressed and associates with high vascular density, high c-erbB-2 expression and extensive nodal metastasis in breast cancer (Giatromanolaki et al., 2006). In a slightly larger study, HIF-2α was associated with ABCG2 expression, histology grade and Ki67 expression in invasive ductal carcinoma (Xiang et al., 2012). Importantly, in two separate breast cancer cohorts, HIF-2α correlate to reduced recurrence-free survival, breast-cancer specific survival and presence of distal metastasis (Helczynska et al., 2008).

Acute myeloid leukemia

Note

Knockdown of HIF-2α in CD34+ acute myeloid leukemia (AML) cells reduce engraftment ability in irradiated mice (Rouault-Pierre et al., 2013). The HIF-2α deficient cells are more susceptible to apoptosis as a result of increased ROS and ER-induced stress indicating that HIF-2α is important for AML cell survival.

Other tumor types

Note

Expression of the HIF-2α protein has also been reported in other solid tumor types including colorectal cancer (Yoshimura et al., 2004), prostate cancer (Boddy et al., 2005), non-small cell lung cancer (Giatromanolaki et al., 2001), squamous cell head-and-neck cancer (Koukourakis et al., 2002), nodular malignant melanoma (Giatromanolaki et al., 2003) and endometrial adenocarcinoma (Sivridis et al., 2002).

Inflammation

Note

Sites of inflammation are often hypoxic due to vascular damage and large infiltration of cells. In order to operate under this condition, cells of the innate immunity adapt by expressing the HIF proteins (Fang et al., 2009; Imtiyaz and Simon, 2010). HIF-2α has been directly coupled to the regulation of proinflammatory cytokine expression in activated macrophages (Fang et al., 2009; Imtiyaz et al., 2010).

Furthermore, HIF-2α has been detected in bone marrow-derived macropahges (BMDMs) and tumor associated macrophages (TAMs) of various human cancers (Talks et al., 2000). Importantly, HIF-2α is essential for TAM migration into tumor lesions (Imtiyaz et al., 2010), which in turn will promote progression and metastasis of tumor cells (Pollard, 2004).

Disease

Erythrocytosis, see section on germinal mutations.

Development

Note

The four available HIF2A knockout mice display substantial differences in phenotype, presumably due to strain background. The first knockout mouse was created on a 129/SvJ background, and resulted in embryonic lethality due to circulatory failure during midgestation (Tian et al., 1997). Two of the following knockout studies demonstrated a role for HIF-2α in vascular development. HIF2A deficient embryos from an ICR/129Sv background die in utero and display severe post-vasculogenic defects (Peng et al., 2000), while HIF2A deficient mice on 129/Sv x Swiss background display lowered VEGF levels (Compernolle et al., 2002). The latter mice are embryonically lethal due to respiratory distress syndrome and cardiac failure (Compernolle et al., 2002). HIF-2α is also important in normal hematopoiesis, as demonstrated by creating adult HIF2A knockout mice by crossing of heterozygous 129S6/SvEvTac EPAS1 and heterozygous C57BL/6J EPAS1 knockout mice (Scortegagna et al., 2003b). These adult HIF2A deficient mice suffer from cardiac hypertrophy, hepatomegaly, oxidative stress and pancytopenia (Scortegagna et al., 2003a). In summary, HIF2A knockout studies demonstrate important roles for HIF-2α in catecholamine synthesis, reactive oxygen species (ROS) homeostasis and vascular remodeling during development.

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