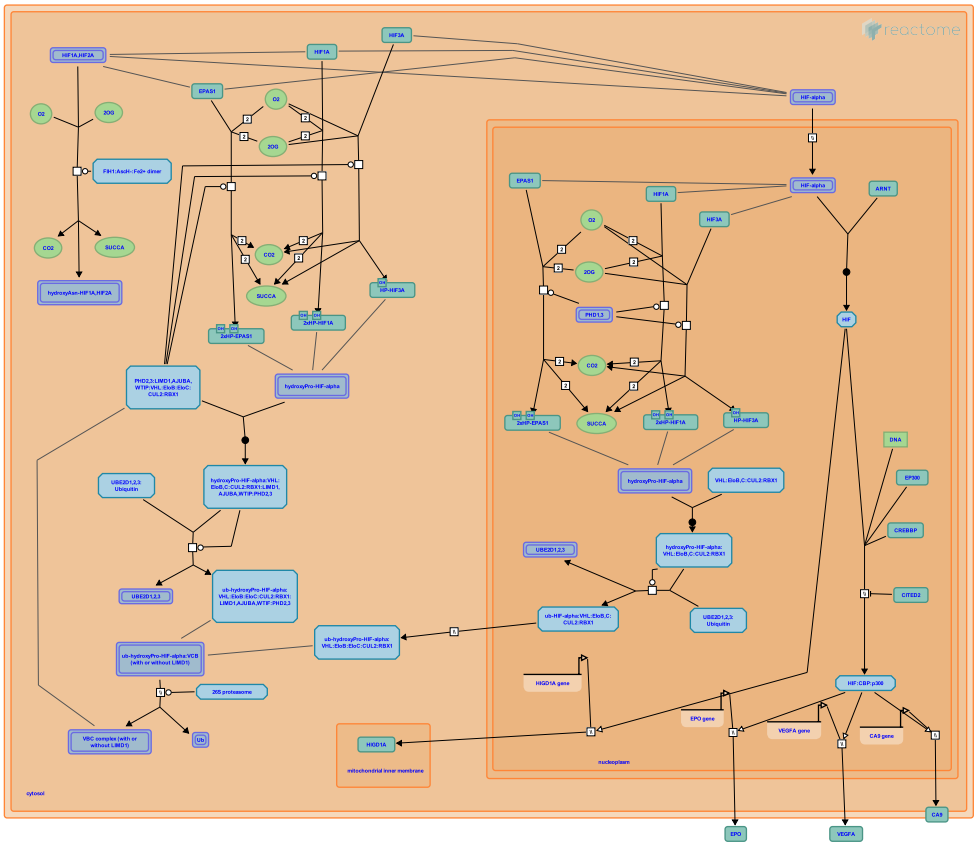
Cellular response to hypoxia



May, B., Rantanen, K.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

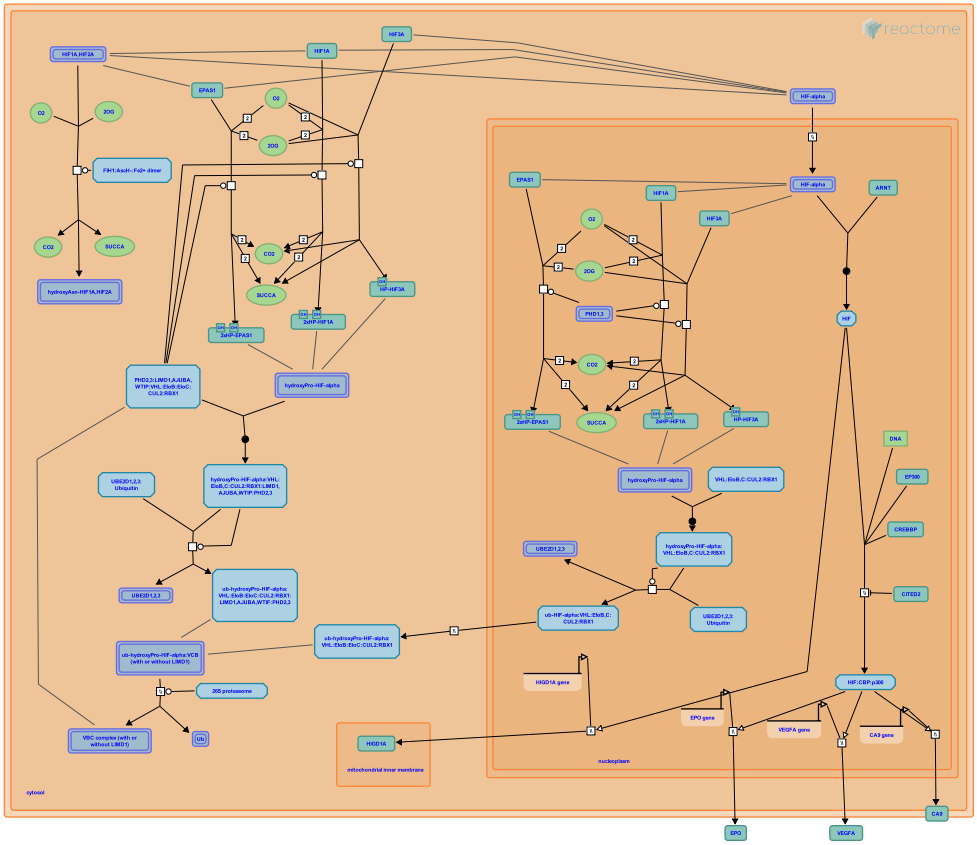
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Cellular response to hypoxia ↗

Stable identifier: R-HSA-1234174

Compartments: cytosol, nucleoplasm



Oxygen plays a central role in the functioning of human cells: it is both essential for normal metabolism and toxic. Here we have annotated one aspect of cellular responses to oxygen, the role of hypoxia-inducible factor in regulating cellular transcriptional responses to changes in oxygen availability.

In the presence of oxygen members of the transcription factor family HIF-alpha, comprising HIF1A, HIF2A (EPAS1), and HIF3A, are hydroxylated on proline residues by PHD1 (EGLN2), PHD2 (EGLN1), and PHD3 (EGLN3) and on asparagine residues by HIF1AN (FIH) (reviewed in Pouyssegur et al. 2006, Semenza 2007, Kaelin and Ratcliffe 2008, Nizet and Johnson 2009, Brahimi-Horn and Pouyssegur 2009, Majmundar et al. 2010, Loenarz and Schofield 2011). Both types of reaction require molecular oxygen as a substrate and it is probable that at least some HIF-alpha molecules carry both hydroxylated asparagine and hydroxylated proline (Tian et al. 2011).

Hydroxylated asparagine interferes with the ability of HIF-alpha to interact with p300 and CBP while hydroxylated proline facilitates the interaction of HIF-alpha with the E3 ubiquitin ligase VHL, causing ubiquitination and proteolysis of HIF-alpha. Hypoxia inhibits both types of hydroxylation, resulting in the stabilization of HIF-alpha, which then enters the nucleus, binds HIF-beta, and recruits p300 and CBP to activate target genes such as EPO and VEGF.

Literature references

Tian, YM., Yeoh, KK., Lee, MK., Eriksson, T., Kessler, BM., Kramer, HB. et al. (2011). Differential sensitivity of HIF hydroxylation sites to hypoxia and hydroxylase inhibitors. *J Biol Chem*. ↗

Kaelin WG, Jr., Ratcliffe, PJ. (2008). Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol Cell, 30*, 393-402. ↗

Majmundar, AJ., Wong, WJ., Simon, MC. (2010). Hypoxia-inducible factors and the response to hypoxic stress. *Mol Cell, 40*, 294-309. ↗

Semenza, GL. (2007). Life with oxygen. *Science, 318*, 62-4. ↗

Loenarz, C., Schofield, CJ. (2011). Physiological and biochemical aspects of hydroxylations and demethylations catalyzed by human 2-oxoglutarate oxygenases. *Trends Biochem Sci, 36*, 7-18. ↗

Editions

2011-03-09	Authored, Edited	May, B.
2012-05-19	Reviewed	Rantanen, K.

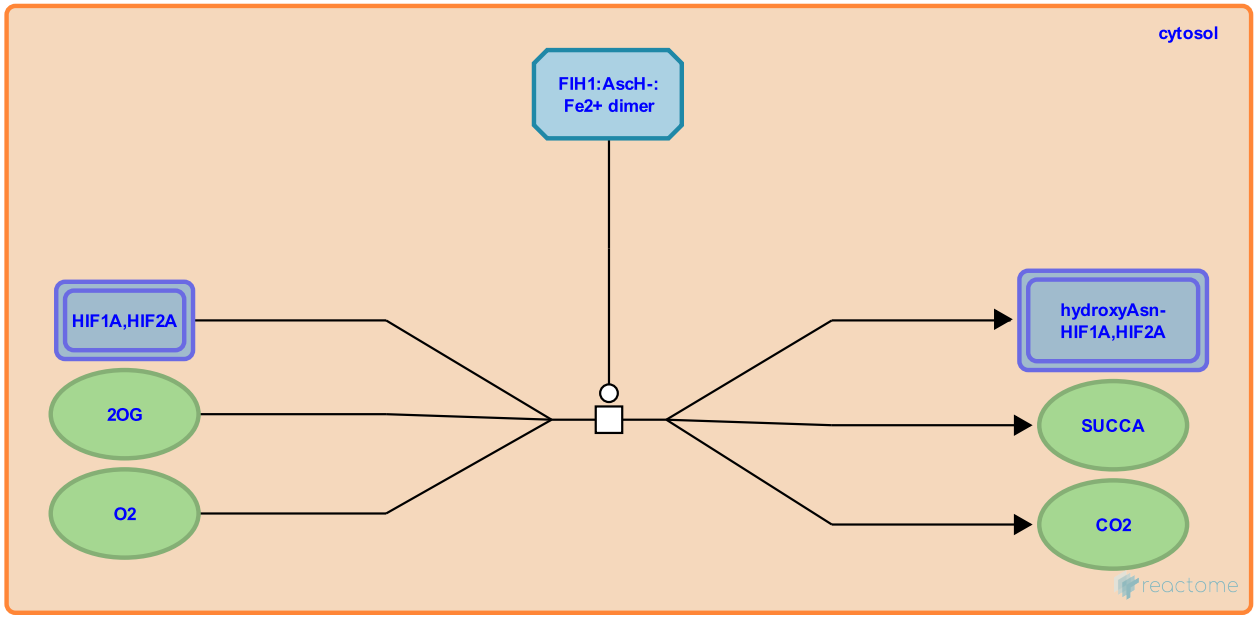
Cytosolic HIF1AN (FIH1) hydroxylates asparagine residues of Hypoxia-inducible Factor Alpha (HIF1A,HIF2A) ↗

Location: Cellular response to hypoxia

Stable identifier: R-HSA-1234164

Type: transition

Compartments: cytosol



HIF1AN (FIH, FIH-1) forms a homodimer that hydroxylates an asparagine residue on HIF1A and HIF2A (Hewitson et al. 2002, Lando et al. 2002, Metzen et al. 2003, Koivunen et al. 2004, Lancaster et al. 2004). The hydroxylation of the asparagine interferes with the interaction between HIF1A/HIF2A and p300, a histone acetylase, and therefore inhibits the ability of HIF1A/2A to activate transcription of target genes (Lando et al. 2002). Because molecular oxygen is a substrate of the reaction, hypoxia is a negative regulator of this reaction and thereby increases transcriptional activation of target genes by HIF1A/2A.

Literature references

Metzen, E., Berchner-Pfannschmidt, U., Stengel, P., Marxsen, JH., Stolze, I., Klinger, M. et al. (2003). Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing. *J Cell Sci, 116*, 1319-26. ↗

Lancaster, DE., McNeill, LA., McDonough, MA., Aplin, RT., Hewitson, KS., Pugh, CW. et al. (2004). Disruption of dimerization and substrate phosphorylation inhibit factor inhibiting hypoxia-inducible factor (FIH) activity. *Biochem J, 383*, 429-37. ↗

Hewitson, KS., McNeill, LA., Riordan, MV., Tian, YM., Bullock, AN., Welford, RW. et al. (2002). Hypoxia-inducible factor (HIF) asparagine hydroxylase is identical to factor inhibiting HIF (FIH) and is related to the cupin structural family. *J Biol Chem, 277*, 26351-5. ↗

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 Dev, 16*, 1466-71. ↗

Koivunen, P., Hirsilä, M., Günzler, V., Kivirikko, KI., Myllyharju, J. (2004). Catalytic properties of the asparaginyl hydroxylase (FIH) in the oxygen sensing pathway are distinct from those of its prolyl 4-hydroxylases. *J Biol Chem, 279*, 9899-904. ↗

Editions

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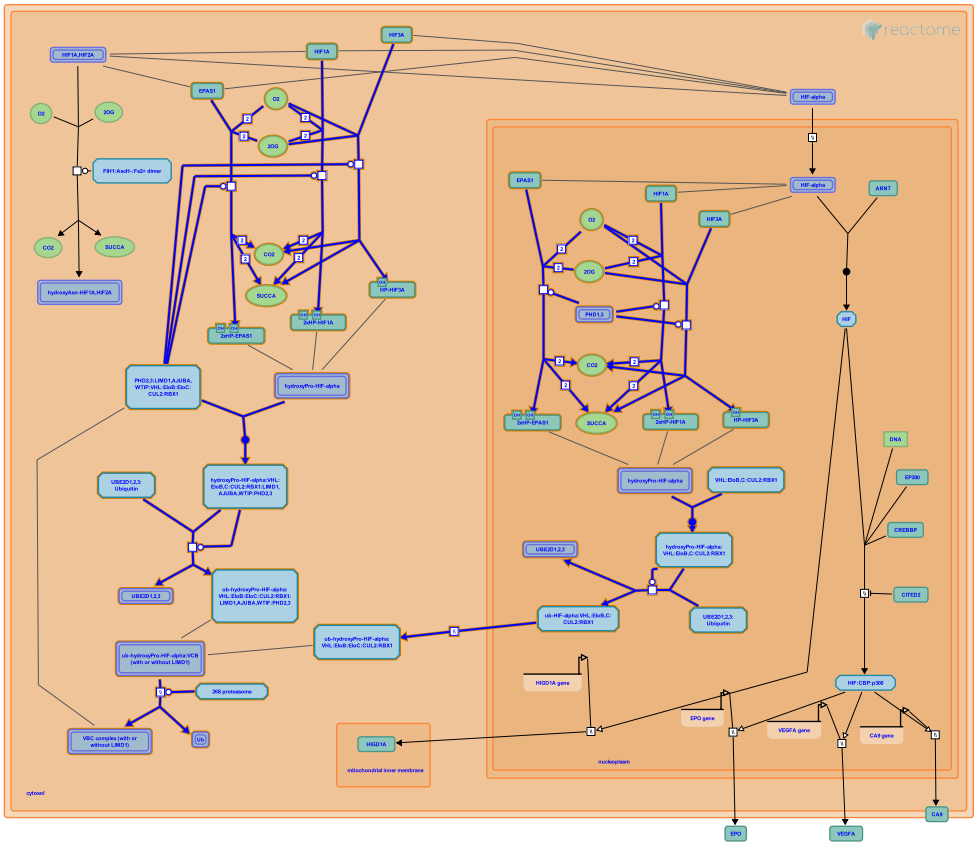
Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha ↗

Location: Cellular response to hypoxia

Stable identifier: R-HSA-1234176

Compartments: cytosol, nucleoplasm



HIF-alpha subunits, comprising HIF1A (Bruick and McKnight 2001, Ivan et al. 2001, Jaakkola et al. 2001), HIF2A (Percy et al. 2008, Furlow et al. 2009), and HIF3A (Maynard et al. 2003), are hydroxylated at proline residues by the prolyl hydroxylases PHD1 (EGLN2), PHD2 (EGLN1), and PHD3 (EGLN3) (Bruick and McKnight 2001, Berra et al. 2003, Hirsila et al. 2003, Metzen et al. 2003, Tuckerman et al. 2004, Appelhoff et al. 2004, Fedulova et al. 2007, Tian et al. 2011). The reaction requires molecular oxygen as a substrate and so it is inhibited by hypoxia. PHD2 (EGLN1) is predominantly cytosolic (Metzen et al. 2003) and is the key determinant in the regulation of HIF-alpha subunits by oxygen (Berra et al. 2003).

HIF-alpha subunits hydroxylated at proline residues are bound by VHL, an E3 ubiquitin ligase in a complex containing ElonginB, Elongin C, CUL2, and RBX1. VHL ubiquitinates HIF-alpha, resulting in destruction of HIF-alpha by proteolysis. Hypoxia inhibits proline hydroxylation and interaction with VHL, stabilizing HIF-alpha, which transits to the nucleus and activates gene expression.

Literature references

Bruick, RK., McKnight, SL. (2001). A conserved family of prolyl-4-hydroxylases that modify HIF. *Science, 294*, 1337-40. ↗

Percy, MJ., Furlow, PW., Lucas, GS., Li, X., Lappin, TR., McMullin, MF. (2008). A gain-of-function mutation in the HIF2A gene in familial erythrocytosis. *N Engl J Med, 358*, 162-8. ↗

Ivan, M., Haberberger, T., Gervasi, DC., Michelson, KS., Günzler, V., Kondo, K. et al. (2002). Biochemical purification and pharmacological inhibition of a mammalian prolyl hydroxylase acting on hypoxia-inducible factor. *Proc Natl Acad Sci U S A, 99*, 13459-64. ↗

Hirsilä, M., Koivunen, P., Günzler, V., Kivirikko, KI., Myllyharju, J. (2003). Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. *J Biol Chem, 278*, 30772-80. ↗

Tuckerman, JR., Zhao, Y., Hewitson, KS., Tian, YM., Pugh, CW., Ratcliffe, PJ. et al. (2004). Determination and comparison of specific activity of the HIF-prolyl hydroxylases. *FEBS Lett, 576*, 145-50. ↗

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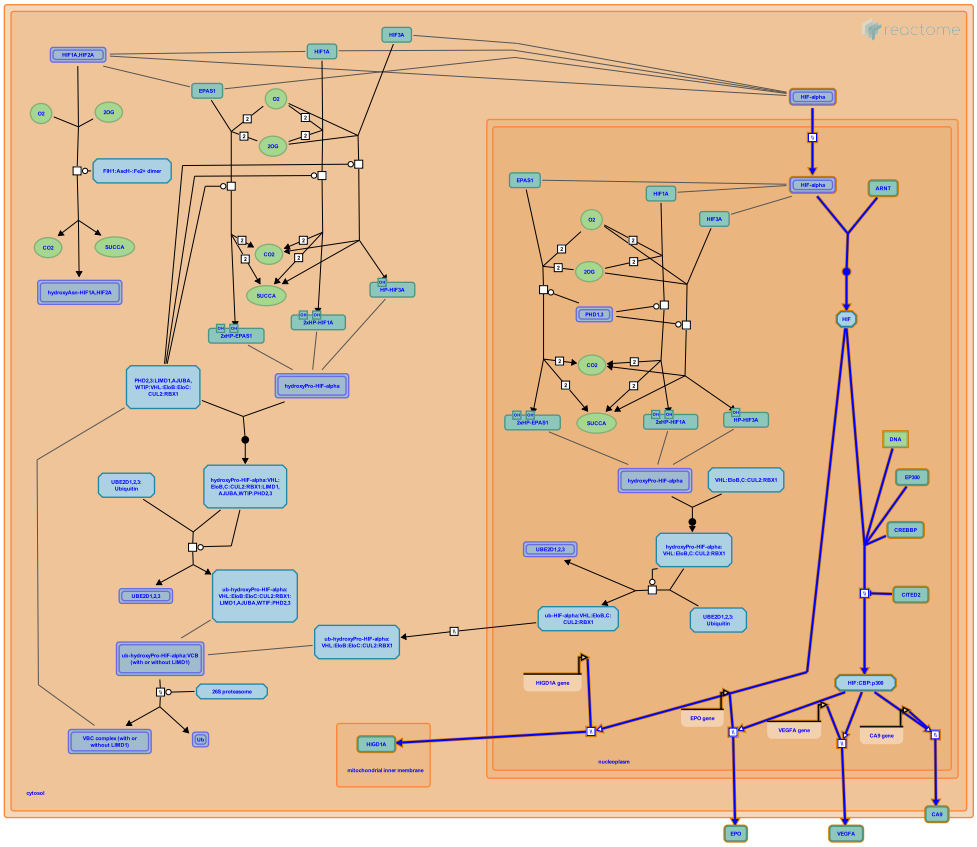
Regulation of gene expression by Hypoxia-inducible Factor ↗

Location: Cellular response to hypoxia

Stable identifier: R-HSA-1234158

Compartments: nucleoplasm



HIF-alpha (HIF1A, HIF2A (EPAS1), HIF3A) is translocated to the nucleus, possibly by two pathways: importin 4/7 (Chachami et al. 2009) and importin alpha/beta (Depping et al. 2008). Once in the nucleus HIF-alpha heterodimerizes with HIF-beta (ARNT) (Wang et al. 1995, Jiang et al. 1996, Tian et al. 1997, Gu et al. 1998, Erbel et al. 2003) and recruits CBP and p300 to promoters of target genes (Ebert and Bunn 1998, Kallio et al. 1998, Ema et al. 1999, Gu et al. 2001, Dames et al. 2002, Freedman et al. 2002).

Literature references

Chachami, G., Paraskeva, E., Mingot, JM., Braliou, GG., Görlich, D., Simos, G. (2009). Transport of hypoxia-inducible factor HIF-1alpha into the nucleus involves importins 4 and 7. *Biochem Biophys Res Commun, 390*, 235-40. ↗

Kallio, PJ., Okamoto, K., O'Brien, S., Carrero, P., Makino, Y., Tanaka, H. et al. (1998). Signal transduction in hypoxic cells: inducible nuclear translocation and recruitment of the CBP/p300 coactivator by the hypoxia-inducible factor-1alpha. *EMBO J, 17*, 6573-86. ↗

Depping, R., Steinhoff, A., Schindler, SG., Friedrich, B., Fagerlund, R., Metzen, E. et al. (2008). Nuclear translocation of hypoxia-inducible factors (HIFs): involvement of the classical importin alpha/beta pathway. *Biochim Biophys Acta, 1783*, 394-404. ↗

Tian, H., McKnight, SL., Russell, DW. (1997). Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells. *Genes Dev, 11*, 72-82. ↗

Jiang, BH., Rue, E., Wang, GL., Roe, R., Semenza, GL. (1996). Dimerization, DNA binding, and transactivation properties of hypoxia-inducible factor 1. *J Biol Chem, 271*, 17771-8. ↗

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