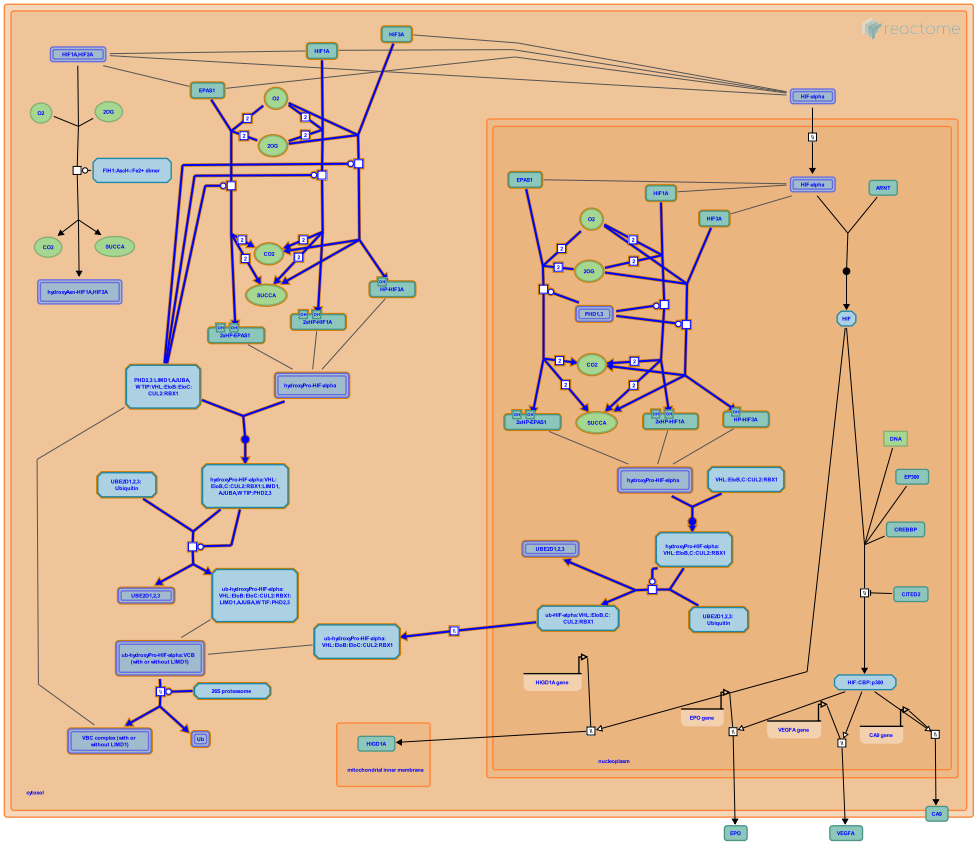
Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha



May, B., Rantanen, K.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

06/05/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

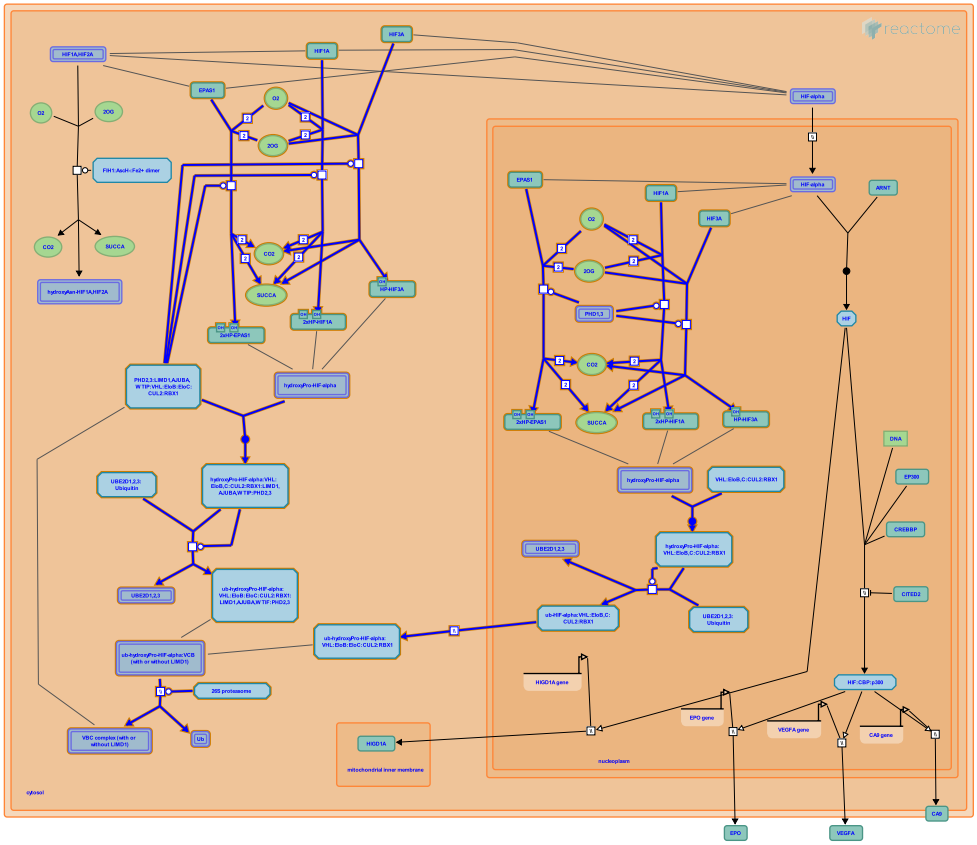
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

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

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

Bergquist, J., Fedulova, N., Hanrieder, J., Emrén, LO. (2007). Expression and purification of catalytically active human PHD3 in Escherichia coli. *Protein Expr Purif, 54*, 1-10. ↗

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Gielbert, J., Gaskell, SJ., Maxwell, PH., Mukherji, M., Pugh, CW., Mole, DR. et al. (2001). Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science, 292*, 468-72. ↗

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

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

Editions

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

Cytosolic PHD2,3 hydroxylates proline residues on EPAS1 (HIF2A) ↗

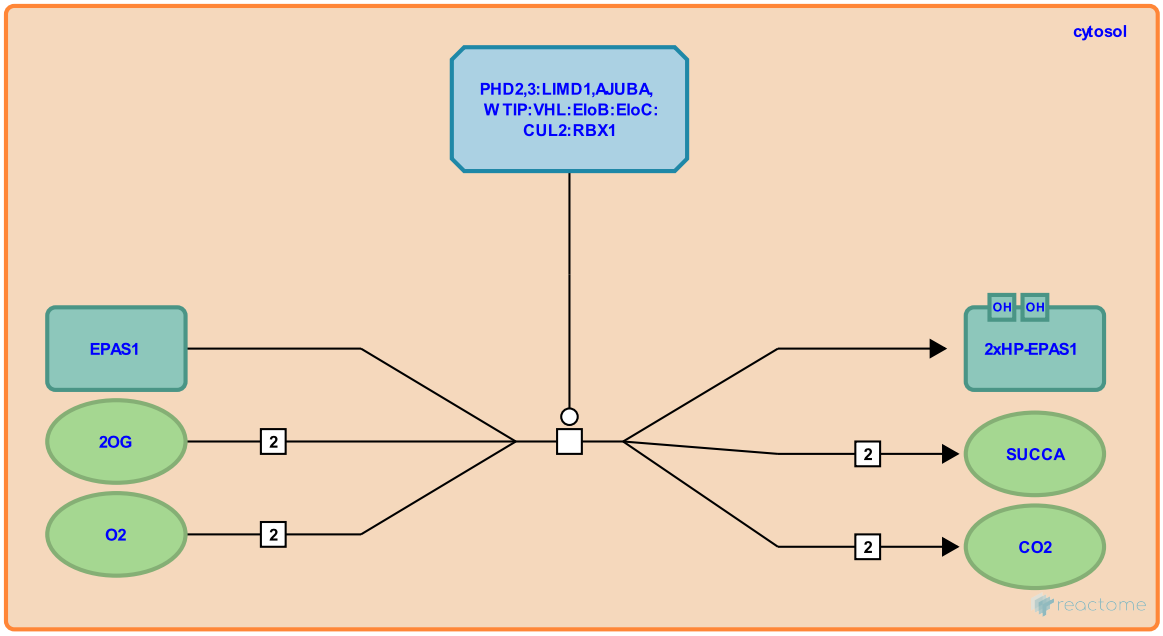
Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234179

Type: transition

Compartments: cytosol

Inferred from: Cytosolic PHD2,3 hydroxylates proline residues on HIF1A (Homo sapiens)



Proline hydroxylases PHD2 (EGLN1) and PHD3 (EGLN3) located in the cytosol (Metzen et al. 2003) hydroxylate EPAS1 (HIF2A) at proline-405 and proline-531 (Hirsila et al. 2003, Percy et al. 2008, Furlow et al. 2009). A portion of PHD3 (EGLN3) is also located in the nucleus (Rantanen et al. 2008).

Followed by: Cytosolic VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Literature references

McMullin, MF., Furlow, PW., Percy, MJ., Lappin, TR., Bierl, C., Master, SR. et al. (2009). Erythrocytosis-associated HIF-2alpha mutations demonstrate a critical role for residues C-terminal to the hydroxylacceptor proline. *J Biol Chem, 284*, 9050-8. ↗

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

Himanen, V., Metzen, E., Högel, H., Rantanen, K., Jaakkola, PM., Pursiheimo, J. (2008). Prolyl hydroxylase PHD3 activates oxygen-dependent protein aggregation. *Mol. Biol. Cell, 19*, 2231-40. ↗

Stengel, P., Klinger, M., Acker, H., Hellwig-Bürgel, T., Fandrey, J., Wotzlaw, C. et al. (2003). Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing. *J Cell Sci, 116*, 1319-26. ↗

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

Editions

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

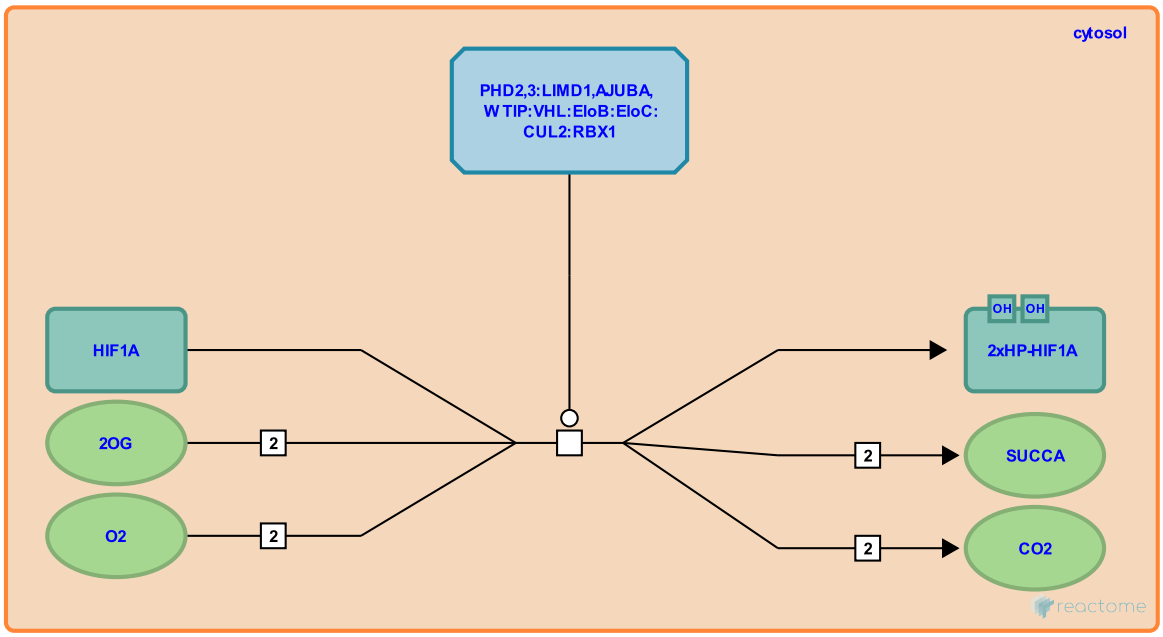
Cytosolic PHD2,3 hydroxylates proline residues on HIF1A ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234177

Type: transition

Compartments: cytosol



Proline hydroxylases PHD2 (EGLN1) and PHD3 (EGLN3) located in the cytosol (Metzen et al. 2003) hydroxylate HIF1A at proline-402 and proline-564 (Bruick and McKnight 2001, Jaakkola et al. 2001, Ivan et al. 2001, Ivan et al. 2002, Berra et al. 2003, Hirsila et al. 2003, Appelhoff et al. 2004, Tuckerman et al. 2004, Fedulova et al. 2007, Tian et al. 2011). A portion of PHD3 (EGLN3) is also located in the nucleus (Rantanen et al. 2008). PHD1, PHD2, and PHD3 are each contained in a complex with LIMD1 and VHL (Foxler et al. 2012).
PHD activity is competitively inhibited by succinate (Selak et al, 2005; Pollard et al, 2005; Koivunen et al, 2007).

Followed by: Cytosolic VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Literature references

Bergquist, J., Fedulova, N., Hanrieder, J., Emrén, LO. (2007). Expression and purification of catalytically active human PHD3 in Escherichia coli. *Protein Expr Purif, 54*, 1-10. ↗

Gielbert, J., Gaskell, SJ., Maxwell, PH., Mukherji, M., Pugh, CW., Mole, DR. et al. (2001). Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science, 292*, 468-72. ↗

Myllyharju, J., Remes, AM., Hirsilä, M., Hassinen, IE., Kivirikko, KI., Koivunen, P. (2007). Inhibition of hypoxia-inducible factor (HIF) hydroxylases by citric acid cycle intermediates: possible links between cell metabolism and stabilization of HIF. *J Biol Chem, 282*, 4524-4532. ↗

Wortham, NC., Griffiths, JR., Moat, SJ., Pollard, PJ., Barclay, E., Barwell, J. et al. (2005). Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. *Hum Mol Genet, 14*, 2231-9. ↗

MacKenzie, ED., Boulahbel, H., Selak, MA., Pan, Y., Armour, SM., Watson, DG. et al. (2005). Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. *Cancer Cell, 7*, 77-85. ↗

Editions

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

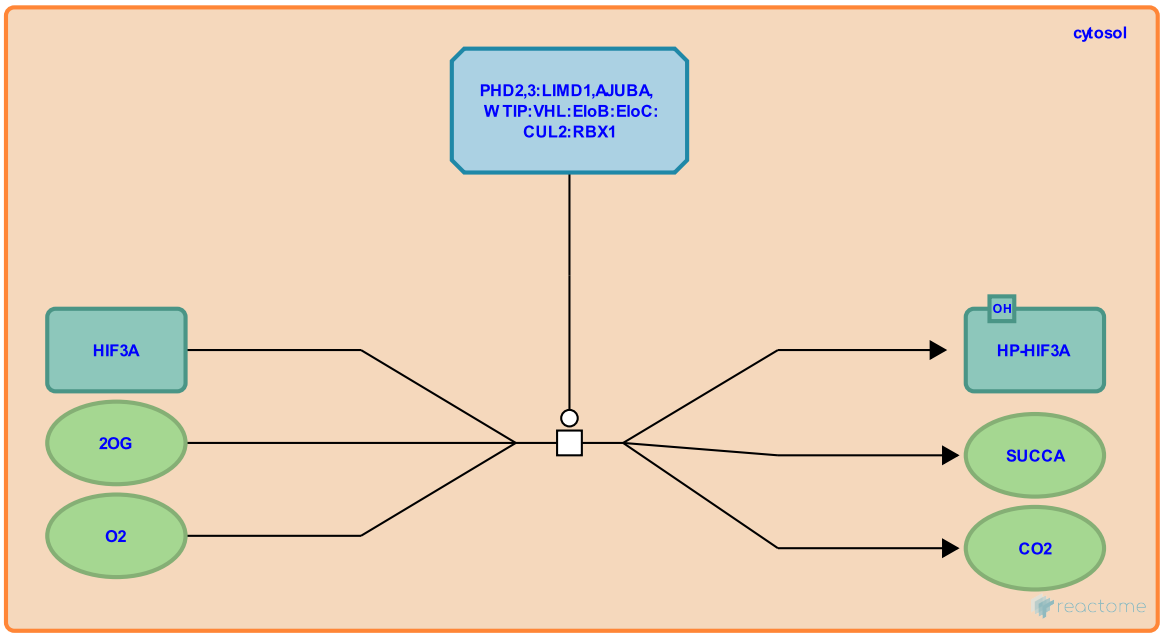
Cytosolic PHD2,3 hydroxylates proline residues on HIF3A ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234173

Type: transition

Compartments: cytosol



Proline hydroxylases PHD2 (EGLN1) and PHD3 (EGLN3) located in the cytosol (Metzen et al. 2003) hydroxylate HIF3A at proline-492 (Hirsila et al. 2003, Maynard et al. 2003). A portion of PHD3 (EGLN3) is also located in the nucleus (Rantanen et al. 2008).

Followed by: Cytosolic VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Literature references

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Himanen, V., Metzen, E., Högel, H., Rantanen, K., Jaakkola, PM., Pursiheimo, J. (2008). Prolyl hydroxylase PHD3 activates oxygen-dependent protein aggregation. *Mol. Biol. Cell, 19*, 2231-40. ↗

Stengel, P., Klinger, M., Acker, H., Hellwig-Bürgel, T., Fandrey, J., Wotzlaw, C. et al. (2003). Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing. *J Cell Sci, 116*, 1319-26. ↗

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

Editions

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

Nuclear PHD1,3 hydroxylates proline residues on EPAS1 (HIF2A)

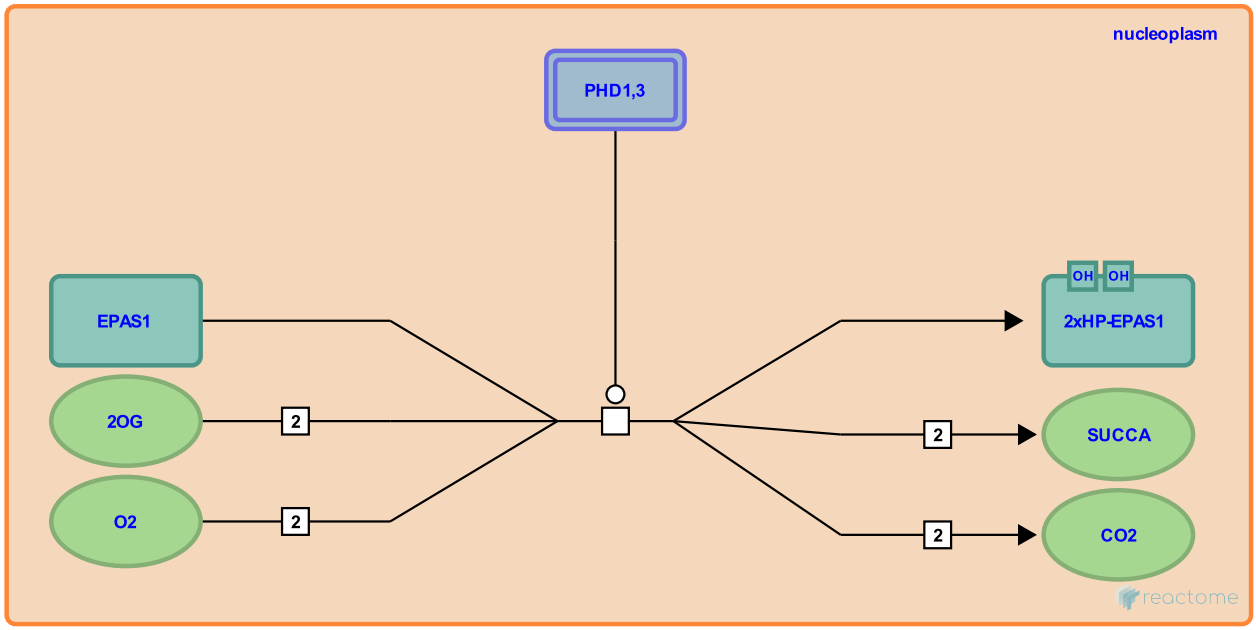
Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234166

Type: transition

Compartments: nucleoplasm

Inferred from: Nuclear PHD1,3 hydroxylates proline residues on HIF1A (Homo sapiens)



Proline hydroxylases PHD1 (EGLN2) and PHD3 (EGLN3) located in the nucleus hydroxylate HIF2A (EPAS1) at proline-405 and proline-531 (Hirsila et al. 2003, Percy et al. 2008, Furlow et al. 2009). The amount of hydroxylation occurring in the nucleus is controversial. Most hydroxylation is believed to be cytosolic.

Followed by: Nuclear VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Literature references

McMullin, MF., Furlow, PW., Percy, MJ., Lappin, TR., Bierl, C., Master, SR. et al. (2009). Erythrocytosis-associated HIF-2alpha mutations demonstrate a critical role for residues C-terminal to the hydroxylacceptor proline. *J Biol Chem, 284*, 9050-8.

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

Stengel, P., Klinger, M., Acker, H., Hellwig-Bürgel, T., Fandrey, J., Wotzlaw, C. et al. (2003). Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing. *J Cell Sci, 116*, 1319-26.

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

Editions

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

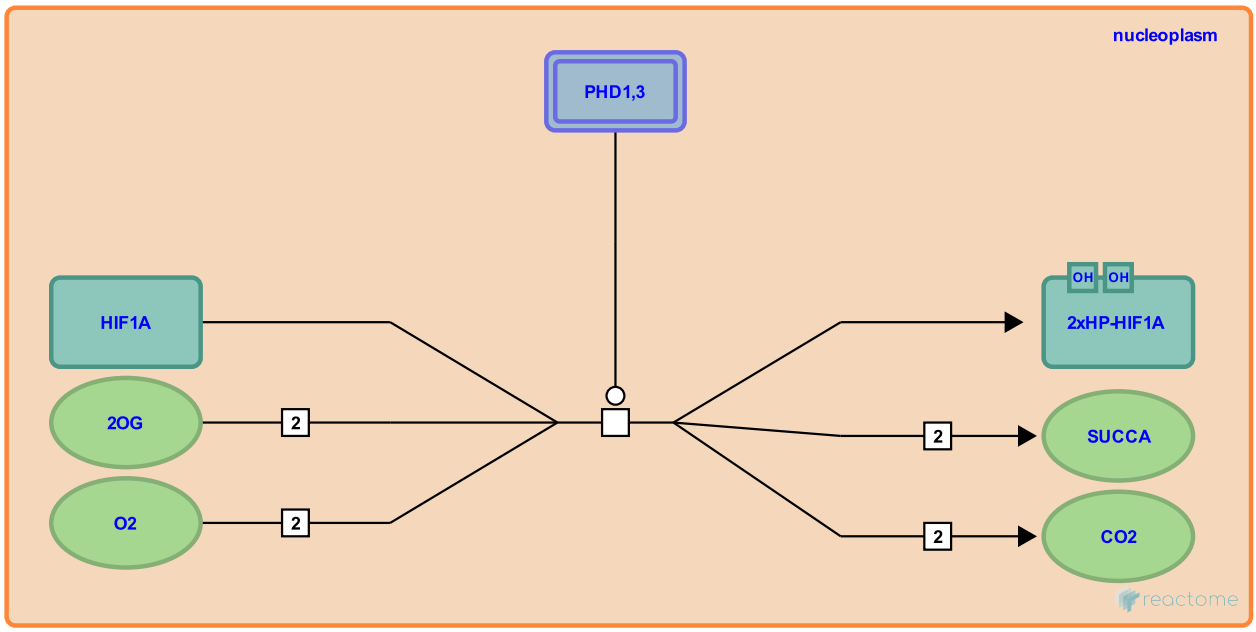
Nuclear PHD1,3 hydroxylates proline residues on HIF1A ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234181

Type: transition

Compartments: nucleoplasm



Proline hydroxylases PHD1 (EGLN2) and PHD3 (EGLN3) located in the nucleus (Metzen et al. 2003) hydroxylate HIF1A at proline-402 and proline-564 (Buick and McKnight 2001, Jaakkola et al. 2001, Ivan et al. 2001, Ivan et al. 2002, Berra et al. 2003, Hirsila et al. 2003, Appelhoff et al. 2004, Tuckerman et al. 2004, Fedulova et al. 2007, Tian et al. 2011). The amount of hydroxylation occurring in the nucleus is controversial. Most hydroxylation is believed to occur in the cytosol.

Followed by: Nuclear VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Literature references

Bergquist, J., Fedulova, N., Hanrieder, J., Emrén, LO. (2007). Expression and purification of catalytically active human PHD3 in Escherichia coli. *Protein Expr Purif, 54*, 1-10. ↗

Günzler, V., Sorokina, I., Gervasi, DC., Haberberger, T., Ivan, M., Kaelin WG, Jr. 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. ↗

Gleadle, JM., Tian, YM., Raval, RR., Harris, AL., Turley, H., Pugh, CW. et al. (2004). Differential function of the prolyl hydroxylases PHD1, PHD2, and PHD3 in the regulation of hypoxia-inducible factor. *J Biol Chem, 279*, 38458-65. ↗

Lane, WS., Asara, JM., Kim, W., Salic, A., Valiando, J., Ivan, M. et al. (2001). HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science, 292*, 464-8. ↗

Gielbert, J., Gaskell, SJ., Maxwell, PH., Mukherji, M., Pugh, CW., Mole, DR. et al. (2001). Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science, 292*, 468-72. ↗

Editions

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

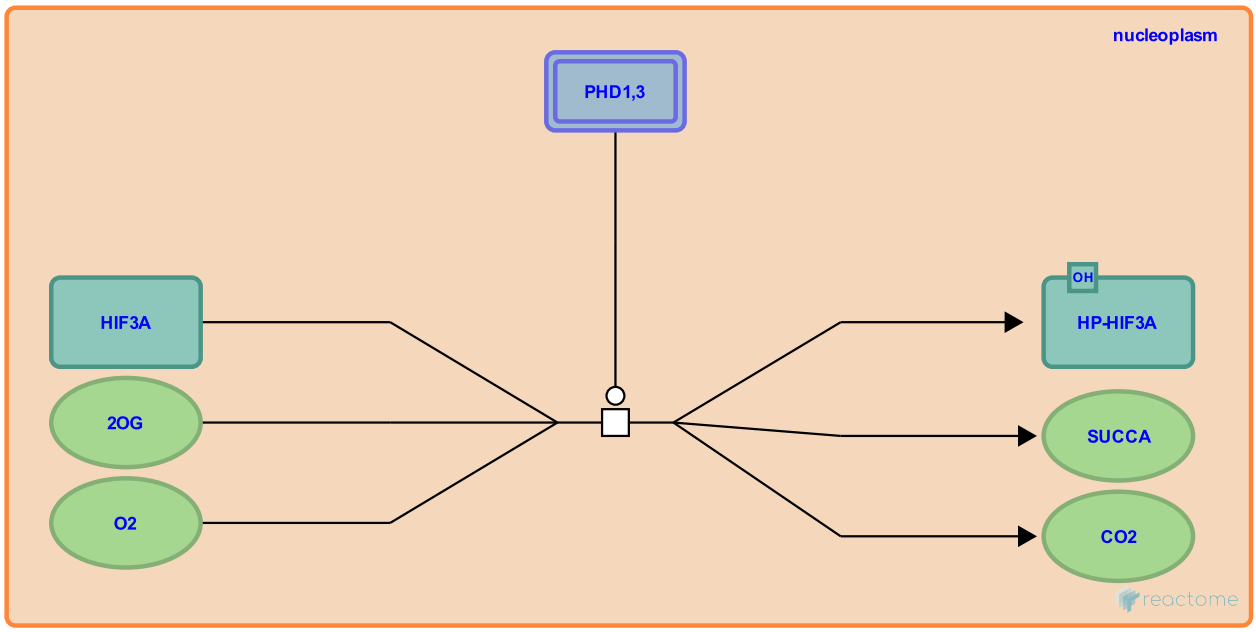
Nuclear PHD1,3 hydroxylates proline residues on HIF3A ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234165

Type: transition

Compartments: nucleoplasm



Proline hydroxylases PHD1 (EGLN2) and PHD3 (EGLN3) located in the nucleus (Metzen et al. 2003) hydroxylate HIF3A at proline-492 (Hirsila et al. 2003, Maynard et al. 2003). Note that proline-492 of the reference isoform is proline-490 in isoform 2, the protein cited by Maynard et al. 2003. The amount of hydroxylation occurring in the nucleus is controversial. Most hydroxylation is believed to occur in the cytosol.

Followed by: Nuclear VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Literature references

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Stengel, P., Klinger, M., Acker, H., Hellwig-Bürgel, T., Fandrey, J., Wotzlaw, C. et al. (2003). Intracellular localisation of human HIF-1 alpha hydroxylases: implications for oxygen sensing. *J Cell Sci, 116*, 1319-26. ↗

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

Editions

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

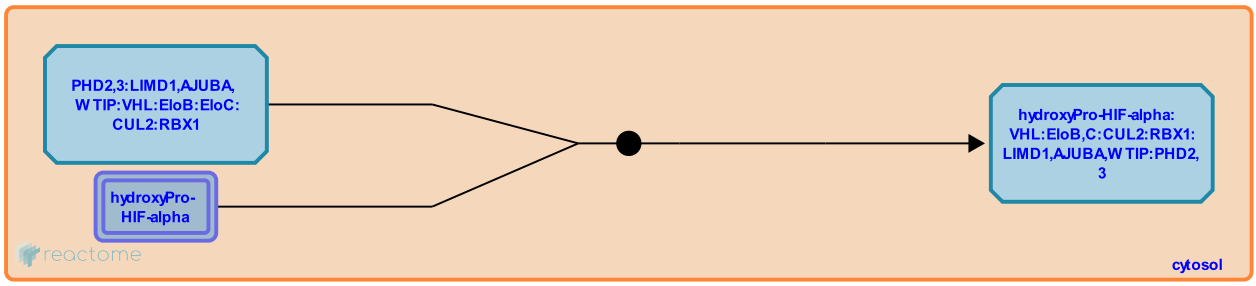
Cytosolic VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234183

Type: binding

Compartments: cytosol



VHL within the VHL:ElonginB:ElonginC:CUL2:RBX1 Complex binds HIF-alpha subunits that have hydroxylated proline residues (Cockman et al. 2000, Ohh et al. 2000, Tanimoto et al. 2000, Jaakkola et al. 2001, Ivan et al. 2001, Yu et al. 2001). VHL constitutively shuttles between the cytosol and nucleoplasm (Lewis and Roberts 2003) and though the VHL:HIF-alpha complex is predominantly nuclear, binding and degradation can occur in both the cytosol and the nucleus (Berra et al. 2001).

Preceded by: Cytosolic PHD2,3 hydroxylates proline residues on HIF3A, Cytosolic PHD2,3 hydroxylates proline residues on HIF1A, Cytosolic PHD2,3 hydroxylates proline residues on EPAS1 (HIF2A)

Followed by: Cytosolic VBC complex ubiquitinylates hydroxyprolyl-HIF-alpha

Literature references

Masson, N., Chang, GW., Mole, DR., Jaakkola, P., Maxwell, PH., Cockman, ME. et al. (2000). Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel-Lindau tumor suppressor protein. *J Biol Chem, 275*, 25733-41. ↗

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Poellinger, L., Pereira, T., Tanimoto, K., Makino, Y. (2000). Mechanism of regulation of the hypoxia-inducible factor-1 alpha by the von Hippel-Lindau tumor suppressor protein. *EMBO J, 19*, 4298-309. ↗

Pavletich, N., Kim, TY., Park, CW., Ivan, M., Kaelin, WG., Ohh, M. et al. (2000). Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol, 2*, 423-7. ↗

Lane, WS., Asara, JM., Kim, W., Salic, A., Valiando, J., Ivan, M. et al. (2001). HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science, 292*, 464-8. ↗

Editions

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

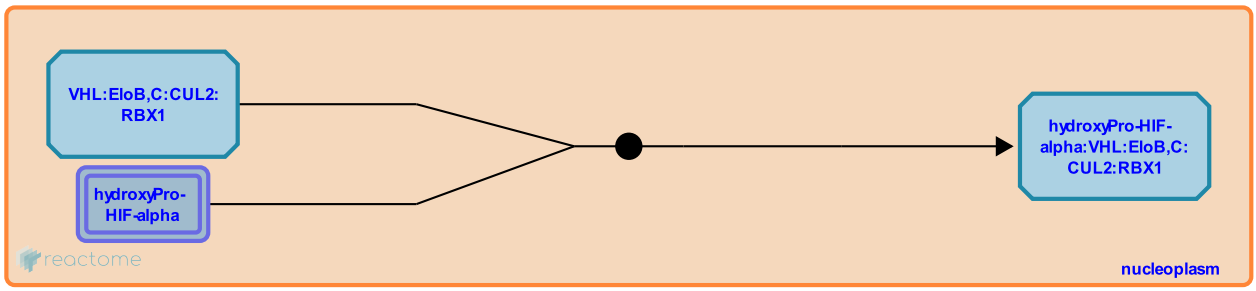
Nuclear VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234169

Type: binding

Compartments: nucleoplasm



The VHL component of the VHL:ElonginB:ElonginC:CUL2:RBX1 binds HIF-alpha that have hydroxylated proline residues (Cockman et al. 2000, Ohh et al. 2000, Tanimoto et al. 2000, Jaakkola et al. 2001, Ivan et al. 2001, Yu et al. 2001, Bonicalzi et al. 2001). The VHL:HIF-alpha complex is predominantly nuclear (Lewis and Roberts 2003) however binding and degradation of HIF-alpha can also occur in the cytosol (Berra et al. 2001).

Preceded by: Nuclear PHD1,3 hydroxylates proline residues on HIF3A, Nuclear PHD1,3 hydroxylates proline residues on HIF1A, Nuclear PHD1,3 hydroxylates proline residues on EPAS1 (HIF2A)

Followed by: Nuclear VBC complex ubiquitinylates HIF-alpha

Literature references

Masson, N., Chang, GW., Mole, DR., Jaakkola, P., Maxwell, PH., Cockman, ME. et al. (2000). Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel-Lindau tumor suppressor protein. *J Biol Chem, 275*, 25733-41. ↗

Lee, S., de Paulsen, N., Groulx, I., Bonicalzi, ME. (2001). Role of exon 2-encoded beta -domain of the von Hippel-Lindau tumor suppressor protein. *J Biol Chem, 276*, 1407-16. ↗

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Poellinger, L., Pereira, T., Tanimoto, K., Makino, Y. (2000). Mechanism of regulation of the hypoxia-inducible factor-1 alpha by the von Hippel-Lindau tumor suppressor protein. *EMBO J, 19*, 4298-309. ↗

Pavletich, N., Kim, TY., Park, CW., Ivan, M., Kaelin, WG., Ohh, M. et al. (2000). Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol, 2*, 423-7. ↗

Editions

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

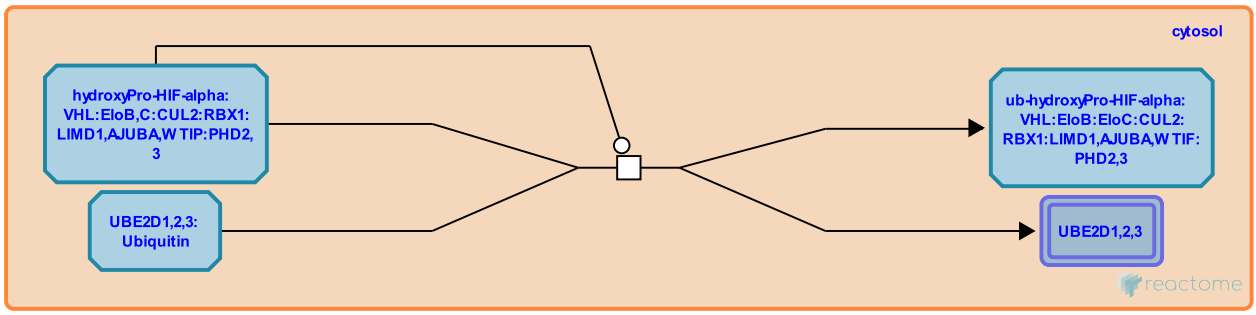
Cytosolic VBC complex ubiquitinylates hydroxyprolyl-HIF-alpha ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234163

Type: transition

Compartments: cytosol



VHL is an E3 ubiquitin ligase that conjugates ubiquitin to hydroxylated HIF-alpha (Iwai et al. 1999, Kamura et al. 2000, Ohh et al. 2000, Groulx and Lee 2002, Maynard et al. 2003). VHL is predominantly cytosolic and shuttles between the cytosol and the nucleus (Lee et al. 1999, Groulx and Lee 2002). Ubiquitination and degradation of HIF-alpha can occur in both the cytosol and the nucleus (Berra et al. 2001).

Preceded by: Cytosolic VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Followed by: Proteasome proteolyzes ub-HIF-alpha

Literature references

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Kamura, T., Sato, S., Czyzyk-Krzeska, M., Conaway, JW., Iwai, K., Conaway, RC. (2000). Activation of HIF1alpha ubiquitination by a reconstituted von Hippel-Lindau (VHL) tumor suppressor complex. *Proc Natl Acad Sci U S A, 97*, 10430-5. ↗

Stearman, R., Pavlakis, GN., Stauber, R., Neumann, M., Klausner, RD., Lee, S. et al. (1999). Transcription-dependent nuclear-cytoplasmic trafficking is required for the function of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 19*, 1486-97. ↗

Pavletich, N., Kim, TY., Park, CW., Ivan, M., Kaelin, WG., Ohh, M. et al. (2000). Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol, 2*, 423-7. ↗

Editions

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

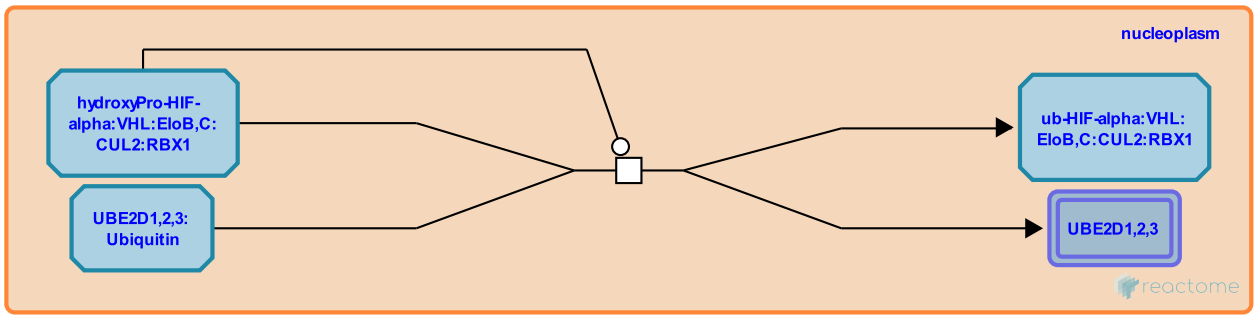
Nuclear VBC complex ubiquitinylates HIF-alpha ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234172

Type: transition

Compartments: nucleoplasm



VHL is an E3 ubiquitin ligase that conjugates ubiquitin to hydroxylated HIF-alpha (Iwai et al. 1999, Kamura et al. 2000, Ohh et al. 2000, Groulx and Lee 2002, Maynard et al. 2003). VHL is predominantly cytosolic and shuttles between the cytosol and the nucleus (Lee et al. 1999, Groulx and Lee 2002). Ubiquitination and degradation of HIF-alpha can occur in both the cytosol and the nucleus (Berra et al. 2001). Upon return to normoxia from hypoxia most ubiquitinated HIF-alpha is nuclear (Groulx and Lee 2002).

Preceded by: Nuclear VHL:EloB,C:CUL2:RBX1 binds hydroxyprolyl-HIF-alpha

Followed by: ub-hydroxyPro-HIF-alpha:VHL:EloB,C:CUL2:RBX1 translocates from the nucleus to the cytosol

Literature references

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Kamura, T., Sato, S., Czyzyk-Krzeska, M., Conaway, JW., Iwai, K., Conaway, RC. (2000). Activation of HIF1alpha ubiquitination by a reconstituted von Hippel-Lindau (VHL) tumor suppressor complex. *Proc Natl Acad Sci U S A, 97*, 10430-5. ↗

Stearman, R., Pavlakis, GN., Stauber, R., Neumann, M., Klausner, RD., Lee, S. et al. (1999). Transcription-dependent nuclear-cytoplasmic trafficking is required for the function of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 19*, 1486-97. ↗

Pavletich, N., Kim, TY., Park, CW., Ivan, M., Kaelin, WG., Ohh, M. et al. (2000). Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol, 2*, 423-7. ↗

Editions

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

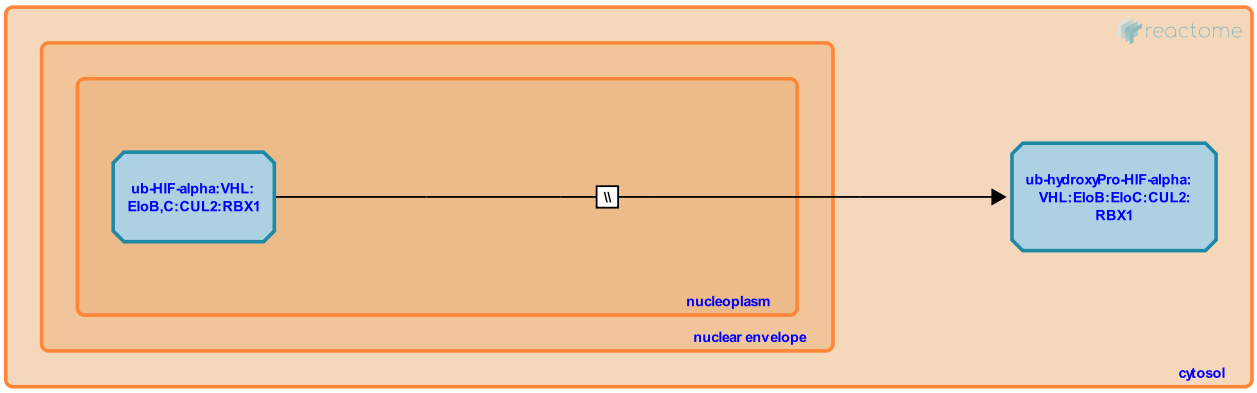
ub-hydroxyPro-HIF-alpha:VHL:EloB,C:CUL2:RBX1 translocates from the nucleus to the cytosol ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234175

Type: omitted

Compartments: nucleoplasm, cytosol



When hypoxic cells return to normoxia, HIF-alpha is ubiquitinated in the nucleus and exported to the cytosol (Groulx and Lee 2002). The shuttling of VHL between the nucleus and cytosol is required (Groulx and Lee 2002, Lee et al. 1999). Different cell types have different nucleocytoplasmic compartmentalization of HIF degradation (Zheng et al. 2006).

Preceded by: Nuclear VBC complex ubiquitinylates HIF-alpha

Followed by: Proteasome proteolyzes ub-HIF-alpha

Literature references

Cao, Y., Salomons, FA., Ruas, JL., Poellinger, L., Pereira, T., Zheng, X. et al. (2006). Cell-type-specific regulation of degradation of hypoxia-inducible factor 1 alpha: role of subcellular compartmentalization. *Mol. Cell. Biol., 26*, 4628-41. ↗

Stearman, R., Pavlakis, GN., Stauber, R., Neumann, M., Klausner, RD., Lee, S. et al. (1999). Transcription-dependent nuclear-cytoplasmic trafficking is required for the function of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 19*, 1486-97. ↗

Lee, S., Groulx, I. (2002). Oxygen-dependent ubiquitination and degradation of hypoxia-inducible factor requires nuclear-cytoplasmic trafficking of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 22*, 5319-36. ↗

Editions

2011-03-09	Authored	May, B.
2011-03-18	Edited	May, B.
2012-05-19	Reviewed	Rantanen, K.

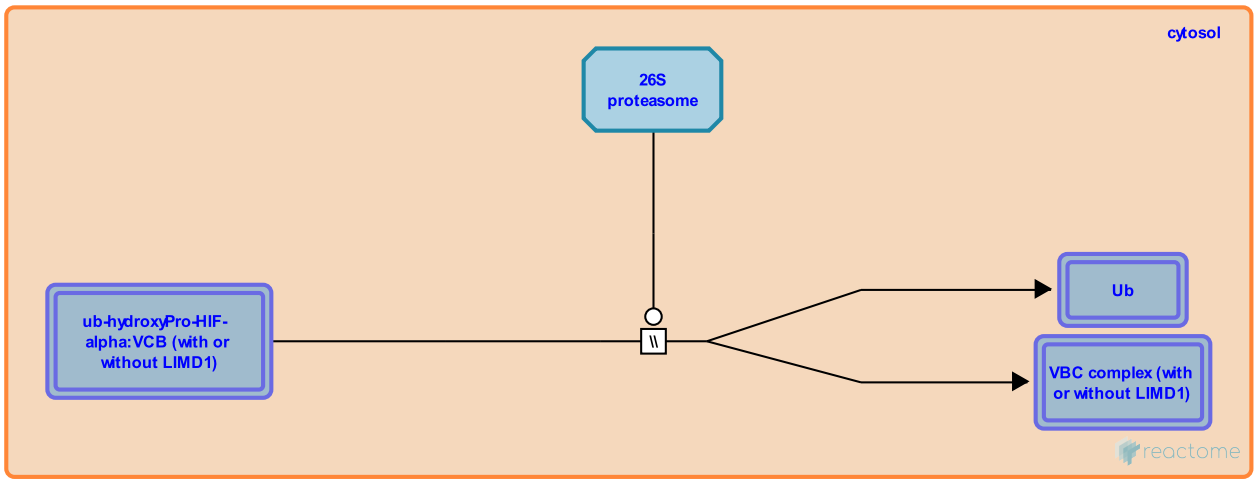
Proteasome proteolyzes ub-HIF-alpha ↗

Location: Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha

Stable identifier: R-HSA-1234159

Type: omitted

Compartments: cytosol



Destruction of ubiquitinated HIF-alpha can occur in both the cytosol and nucleus (Berra et al. 2001). Upon reoxygenation of hypoxic cells HIF-alpha is ubiquitinated in the nucleus and transported to the cytosol in a complex with VHL:ElonginB:ElonginC:CUL2:RBX1 where it is destroyed (Groulx and Lee 2002, Jaakkola et al. 2001, Ivan et al. 2001)

Preceded by: ub-hydroxyPro-HIF-alpha:VHL:EloB,C:CUL2:RBX1 translocates from the nucleus to the cytosol, Cytosolic VBC complex ubiquitinylates hydroxyprolyl-HIF-alpha

Literature references

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Lane, WS., Asara, JM., Kim, W., Salic, A., Valiando, J., Ivan, M. et al. (2001). HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science, 292*, 464-8. ↗

Gielbert, J., Gaskell, SJ., Maxwell, PH., Mukherji, M., Pugh, CW., Mole, DR. et al. (2001). Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science, 292*, 468-72. ↗

Lee, S., Groulx, I. (2002). Oxygen-dependent ubiquitination and degradation of hypoxia-inducible factor requires nuclear-cytoplasmic trafficking of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 22*, 5319-36. ↗

Editions

2011-03-18	Authored, Edited	May, B.
2012-05-19	Reviewed	Rantanen, K.

Table of Contents