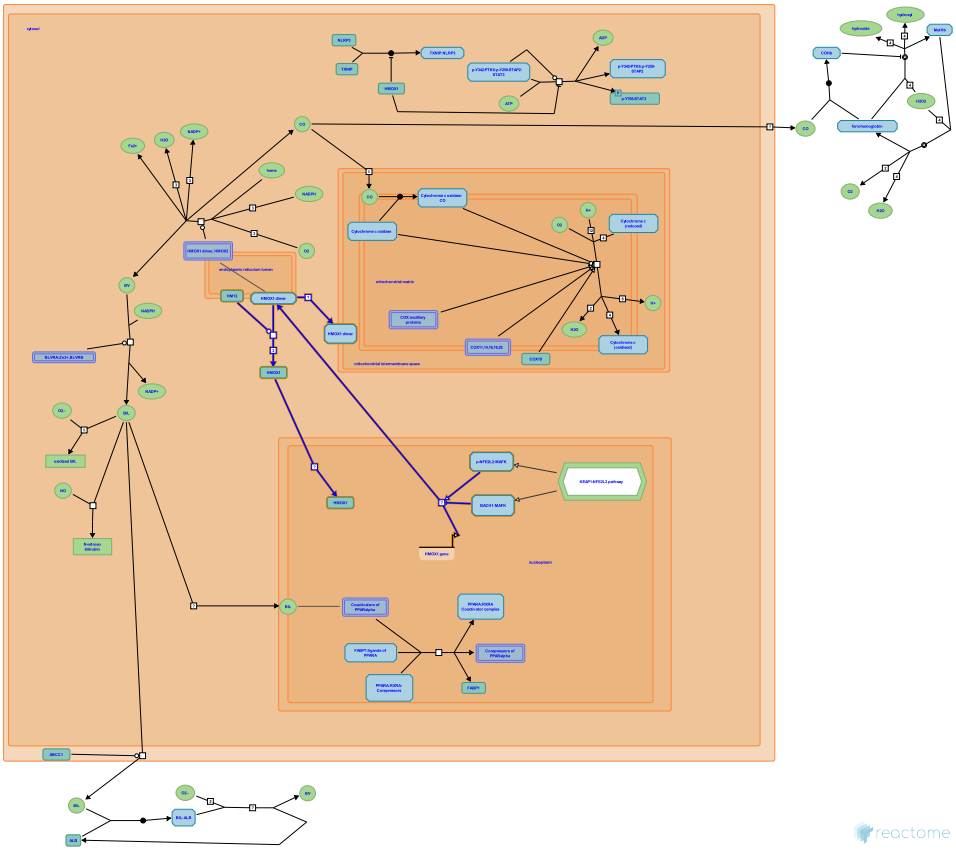
Regulation of HMOX1 expression and activity



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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.
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. ↗

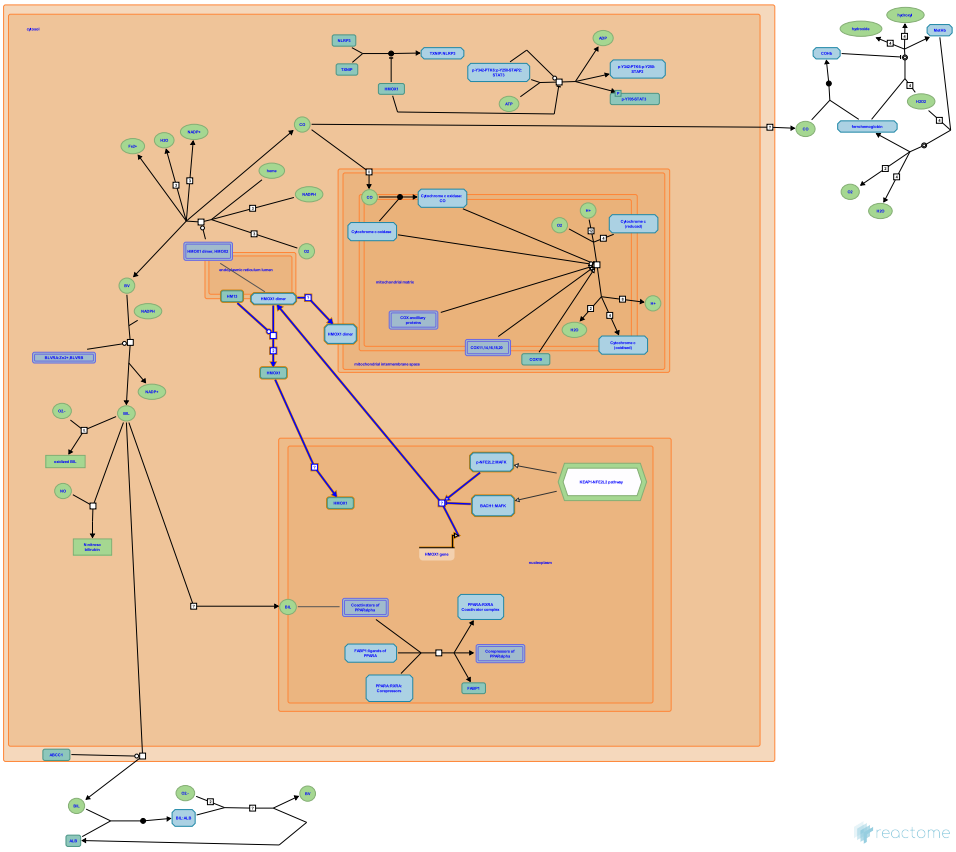
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Regulation of HMOX1 expression and activity ↗

Stable identifier: R-HSA-9707587



Heme oxygenase 1 (HMOX1) is regulated at the level of gene transcription, mRNA translation, localization and degradation. Its gene is often activated under a wide range of stressful conditions. The transcriptional control of HMOX1 is determined by inducible regulatory elements localized in the 5′ region of the promoter, so called antioxidant response elements (ARE)(Raghunath et al, 2018).

AREs on the HMOX1 gene are ultimately controlled by the enhancing NFE2L2:MAFK dimer and the repressing BACH1:MAFK dimer, both of which are influenced by a multitude of processes. Less specific enhancement occurs via AP-1 (FOS:JUN) dimers (Funes et al, 2020).

HMOX1 activity depends on dimerization in the ER membrane. Its membrane localization is abandoned by cleavage of the membrane domain by HM13. The resulting soluble enzyme is found in the cytosol, mitochondria, and the nucleus (Schaefer et al, 2017).

Literature references

Sethi, G., Kumar, AP., Sundarraj, K., Perumal, E., Arfuso, F., Raghunath, A. et al. (2018). Antioxidant response elements: Discovery, classes, regulation and potential applications. *Redox Biol, 17,* 297-314. ↗

Behrends, S., Schaefer, B., Moriishi, K. (2017). Insights into the mechanism of isoenzyme-specific signal peptide peptidase-mediated translocation of heme oxygenase. *PLoS One, 12,* e0188344. ↗

Kalergis, AM., Fernández-Fierro, A., Funes, SC., Mackern-Oberti, JP., Bueno, SM., Covián, C. et al. (2020). Naturally Derived Heme-Oxygenase 1 Inducers and Their Therapeutic Application to Immune-Mediated Diseases. *Front Immunol, 11,* 1467. ↗

Alam, J., Choi, AM., Ryter, SW. (2006). Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiol Rev, 86,* 583-650. ↗

Editions

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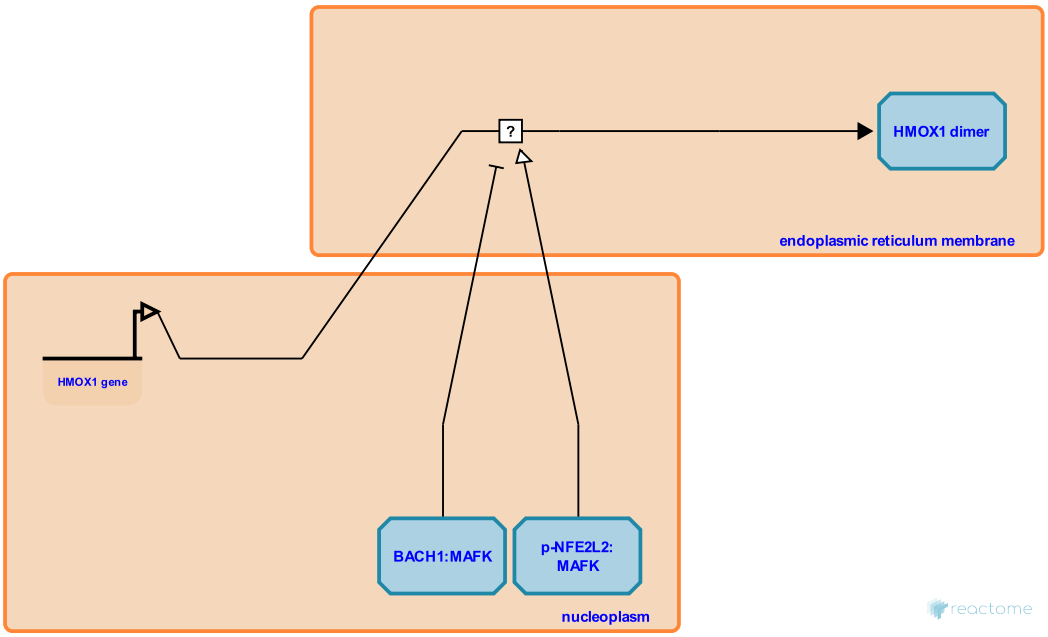
HMOX1 gene produces HMOX1 dimer ↗

Location: Regulation of HMOX1 expression and activity

Stable identifier: R-HSA-9707645

Type: uncertain

Compartments: endoplasmic reticulum membrane, nucleoplasm



Transcription regulator protein BACH1 is a critical physiological repressor of heme oxygenase 1 (HMOX1). BACH1 binds to the multiple Maf recognition elements (MAREs) of HMOX1 enhancer MafK in vitro and represses its activity in vivo. BACH1 is inducible by hypoxia and IFN-gamma (Kitamuro et al, 2003; Sun et al, 2002).

NFE2L2 (nuclear factor erythroid 2-related factor 2) is a transcription factor that activates transcription of a battery of cytoprotective genes by binding to the ARE (antioxidant response element). It is considered not only as a cytoprotective factor regulating the expression of genes coding for anti-oxidant, anti-inflammatory and detoxifying proteins, but it is also a powerful modulator of species longevity. HMOX1 is one of the genes whose expression it activates (Huang et al, 2000; Reichard et al, 2007).

Followed by: HM13 cleaves HMOX1 dimer, HMOX1 dimer translocates from ER membrane to mitochondrial outer membrane

Literature references

Sun, J., Muto, A., Takaku, K., Suzuki, H., Takahashi, S., Taketo, MM. et al. (2002). Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. *EMBO J, 21*, 5216-24. ↗

Sun, J., Takeda, K., Shirato, K., Nakayama, M., Shibahara, S., Fujita, H. et al. (2003). Bach1 functions as a hypoxia-inducible repressor for the heme oxygenase-1 gene in human cells. *J Biol Chem, 278*, 9125-33. ↗

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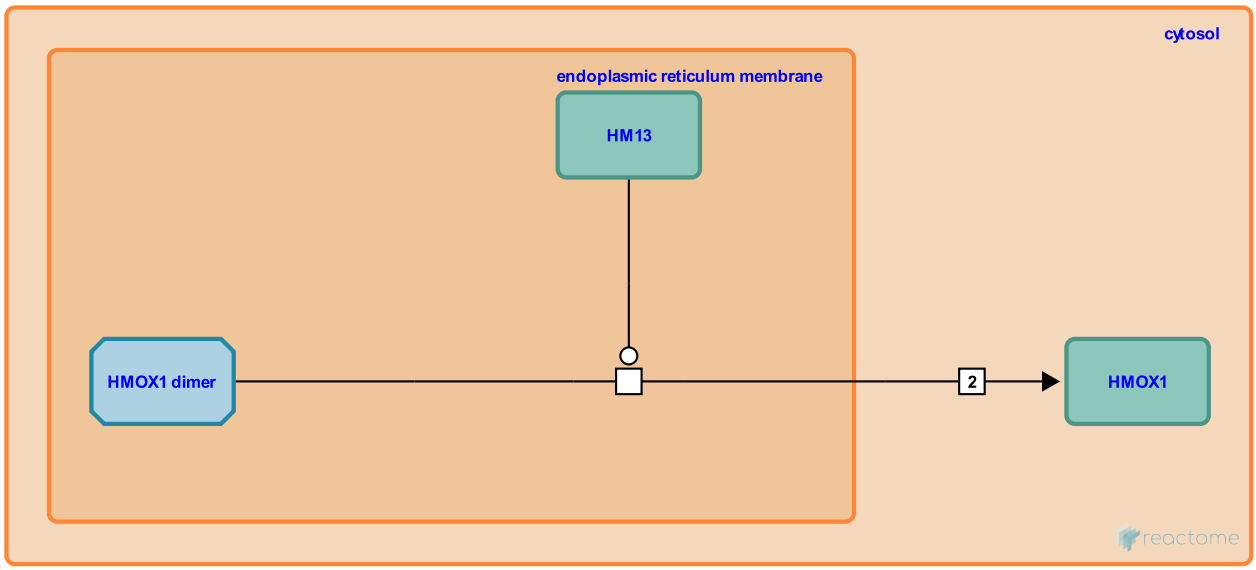
HM13 cleaves HMOX1 dimer ↗

Location: Regulation of HMOX1 expression and activity

Stable identifier: R-HSA-9708457

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Cleavage of heme oxygenase 1 (HMOX1) by HM13 (Signal peptide peptidase) takes place in the ER membrane and removes the membrane domain from HMOX1, making it soluble in the cytosol. The reaction only occurs under conditions of hypoxia (Schaefer et al, 2017; Boname et al, 2014).

Preceded by: HMOX1 gene produces HMOX1 dimer

Followed by: HMOX1 translocates from the cytosol to the nucleoplasm

Literature references

Smith, DL., Smith, JC., Nathan, JA., Wandel, MP., Thurston, TL., Bloor, S. et al. (2014). Cleavage by signal peptide peptidase is required for the degradation of selected tail-anchored proteins. *J Cell Biol, 205*, 847-62. ↗

Behrends, S., Schaefer, B., Moriishi, K. (2017). Insights into the mechanism of isoenzyme-specific signal peptide peptidase-mediated translocation of heme oxygenase. *PLoS One, 12*, e0188344. ↗

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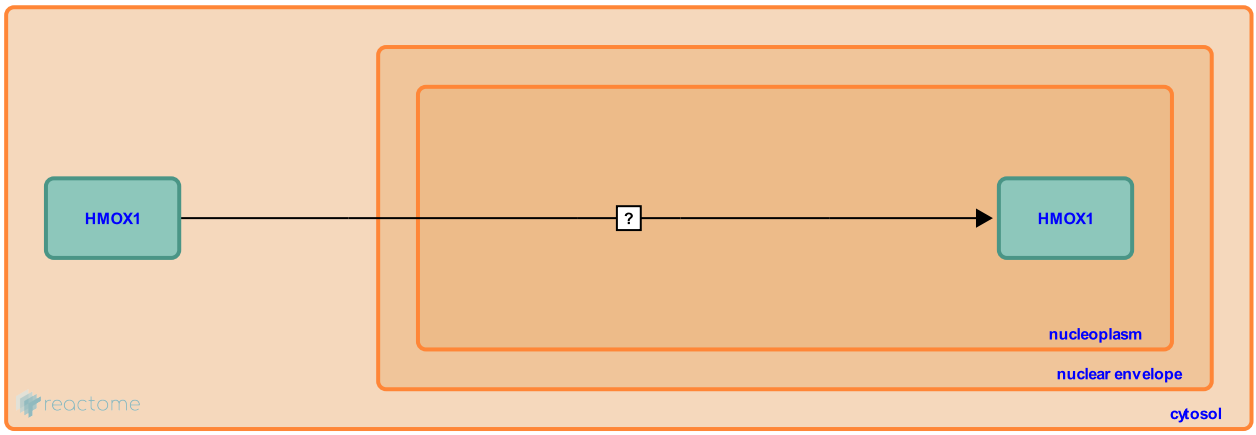
HMOX1 translocates from the cytosol to the nucleoplasm ↗

Location: Regulation of HMOX1 expression and activity

Stable identifier: R-HSA-9708536

Type: uncertain

Compartments: nucleoplasm, cytosol



After exposure to hypoxia and heme or heme/hemopexin, soluble heme oxygenase 1 (HMOX1) is detected in the nucleus. Nuclear localization is also associated with reduction of HMOX1 activity. HMOX1 protein, whether it s enzymatically active or not, mediates activation of oxidant-responsive transcription factors, including activator protein-1 (AP-1). Nevertheless, nuclear HMOX1 protects cells against hydrogen peroxide-mediated injury equally as well as cytoplasmic HMOX1 (Lin et al, 2007).

Preceded by: HM13 cleaves HMOX1 dimer

Literature references

Rish, K., Helston, R., Yang, G., Weng, YH., Polte, T., Lin, Q. et al. (2007). Heme oxygenase-1 protein localizes to the nucleus and activates transcription factors important in oxidative stress. *J Biol Chem, 282*, 20621-33. ↗

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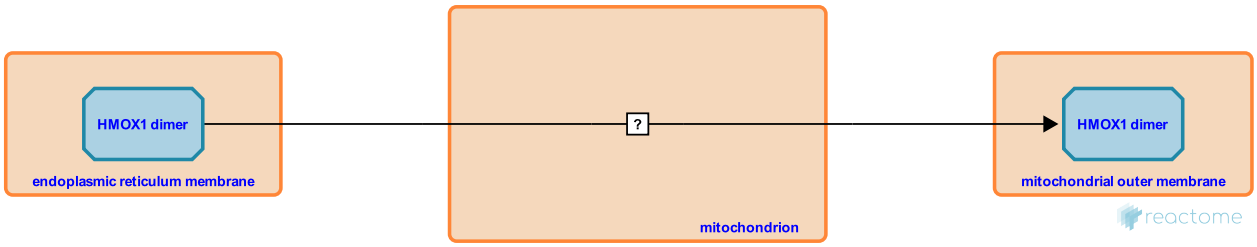
HMOX1 dimer translocates from ER membrane to mitochondrial outer membrane ↗

Location: Regulation of HMOX1 expression and activity

Stable identifier: R-HSA-9708558

Type: uncertain

Compartments: mitochondrion, cytosol



Heme oxygenase 1 (HMOX1) expression increases dramatically in cytosolic and mitochondrial fractions of human alveolar (A549), or bronchial epithelial cells (Beas-2b) exposed to either heme, lipopolysaccharide, or cigarette smoke extract (CSE). Mitochondrial localization of HMOX1 is also observed in a primary culture of human small airway epithelial cells (Siebos et al, 2007).

Preceded by: HMOX1 gene produces HMOX1 dimer

Literature references

Guo, F., van der Toorn, M., Karlsson, JM., Ryter, SW., Postma, DS., Kim, HP. et al. (2007). Mitochondrial localization and function of heme oxygenase-1 in cigarette smoke-induced cell death. *Am J Respir Cell Mol Biol, 36*, 409-17. ↗

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