Induction of heme oxygenase-1 Expression

Subjects: Immunology Contributor: Diego Costa

Heme oxygenase-1 (HO-1) catalyzes the degradation of heme molecules releasing equimolar amounts of biliverdin, iron and carbon monoxide. Its expression is induced in response to stress signals such as reactive oxygen species and inflammatory mediators with antioxidant, anti-inflammatory and immunosuppressive consequences for the host. Interestingly, several intracellular pathogens responsible for major human diseases have been shown to be powerful inducers of HO-1 expression in both host cells and in vivo. Studies have shown that this HO-1 response can be either host detrimental by impairing pathogen control or host beneficial by limiting infection induced inflammation and tissue pathology. These properties make HO-1 an attractive target for host-directed therapy (HDT) of the diseases in question, many of which have been difficult to control using conventional antibiotic approaches.

Keywords: heme oxygenase-1 ; inflammation ; immune response ; infectious disease ; intracellular pathogens ; host directed therapy

1. Introduction

Heme oxygenases (HOs) are highly conserved enzymes that are present in a large number of species as evolutionary distant as algae and humans ^[1]. The mechanisms associated with the catabolism of heme by the heme oxygenase system were first demonstrated in 1968 by Tenhunen et al. utilizing microsomes from rat livers ^[2]. HO itself was first purified in 1977 by Maines et al. ^[3] and almost 10 years later, in 1986, the same author identified two isoforms of the enzyme in rat liver microsomes: heme oxygenase-1 (HO-1), whose expression in liver was upregulated in response to in vivo treatment of rats with chemicals, and heme oxygenase-2 (HO-2), whose constitutive expression remained unaltered by in vivo challenge with the same compounds ^[4]. In parallel, different groups identified a 32 kDa stress-responsive protein, whose expression was highly upregulated in different cell lines in response to challenges such as hyperthermia, heavy metals and oxidative stress. This protein, referred to as Heat-Shock Protein 32 (HSP-32) at that time ^{[S][6][2][8][9][10]}, was later shown to be identical to HO-1 ^{[11][12]}. A third isoform, heme oxygenase-3 (HO-3), was characterized in 1997 in a number of different rat tissues, but displayed poor enzymatic activity ^[13] and its physiological role remains largely uncharacterized to this day. A later study in 2004 failed to isolate rat HO-3 protein and questioned the existence of its gene speculating that the originally identified HO-3 may in fact represent the product of pseudogenes derived from HO-2 transcripts ^[14].

The main function of HO-1 and HO-2 is to catalyze the degradation of heme molecules, providing the rate-limiting step for this reaction, which consumes three molecules of O_2 and seven electrons resulting in the release of equimolar amounts of carbon monoxide (CO), ferrous iron (Fe²⁺) and biliverdin ^[15]. Both HO-1 and HO-2 have a conserved heme catalytic domain, while HO-2 has two additional heme-binding regions, which are associated with regulation of its activity, but are devoid of enzymatic function ^[16]. It has recently been determined that these regions play a role in the transfer of heme molecules to the catalytic site ^[17]. After heme binds to HO, the first step of the degradation reaction uses an O₂ molecule and electrons donated by NADPH–cytochrome-P450-reductase to oxidize heme into α-meso-hydroxyheme, releasing a water molecule. α-meso-hydroxyheme further reacts with another oxygen molecule resulting in the release of verdoheme and CO. A subsequent reaction step consumes a third O₂ molecule and again electrons donated by NADPH–cytochrome-P450-reductase, converting verdoheme into biliverdin and ferrous iron ^[18].

In homeostatic conditions, HO-1 is detected mainly in the liver and spleen, while HO-2 is stably expressed in most organs with higher levels being found in testes, spleen, liver, kidney, cardiovascular and central nervous systems ^{[19][20]}. Unlike HO-2, whose expression remains unchanged after challenge with different stressors ^[16], HO-1 expression is induced in cells from most tissues in response to oxidative stress and inflammation and is particularly highly upregulated in macrophages affected by infection with intracellular microorganisms ^{[21][22]}.

Heme and the products of its degradation can influence the outcome of infection with intracellular pathogens in different ways. Heme can be used as a source of nutrient iron for replication by intracellular pathogens, directly enhancing their survival and growth inside their host cell niches including phagocytes ^[23]. On the other hand, the CO and bilverdin products of heme degradation can exert both pro and anti-inflammatory roles, resulting in the suppression of immune responses and control of pathogen replication, or in the regulation of pathogenesis and inflammation-driven tissue damage ^{[24][25]}. In the center of this process lies the inducible HO-1 isoform, which by mediating heme degradation can markedly influence the outcome of infection with intracellular pathogens through the diverse effects of it enzymatic products ^[26]. Due to its close association with the inflammatory process, numerous studies have evaluated the use of HO-1 as a biomarker for severity or prognosis of such infectious diseases. This work has been accompanied by mechanistic studies examining the role of HO-1 in both host resistance and pathogenesis employing genetically deficient animals or pharmacological inhibitors or inducers of the enzyme's activity or expression as investigative tools.

2. Mechanisms of Induction of HO-1 Expression

HO-1 is constitutively expressed at high levels in the liver and spleen reticuloendothelial systems, especially in macrophages that engulf senescent red blood cells and promote, through the action of HO-1, the recycling of iron from heme derived from hemoglobin ^[27]. Heme can also originate from degradation of other heme containing proteins such as myoglobin, cytochromes and several peroxidases, catalases and oxidases ^[28], or can be internalized from the extracellular compartment, where free heme and hemoglobin molecules are scavenged by the acute phase proteins hemopexin and haptoglobin respectively and then endocytosed via interaction with the receptors CD91 (heme/hemopexin complex) and CD163 (hemoglobin/haptoglobin complex) ^{[29][30]}. Heme is transported from the phagolysosomes to cytosol by the heme responsive gene-1 (HRG-1 or SLC48A1) transporter ^{[31][32]} and later to the nucleus where it can directly induce HO-1 expression by playing a pivotal role in a sequence of events that culminate in HMOX1 gene transcription as described below. The mechanisms involved in its transport to the nucleus, however, are not completely understood, although there is evidence identifying the enzyme biliverdin reductase as a mediator in this process ^[33].

The HMOX1 gene contains in its promoter region a motif known as Maf Recognition Element (MARE) or Antioxidant Response Element (ARE), which is recognized by a dimer composed of the BTB and CNC Homology 1 (BACH1) transcription factor together with one of 3 small Maf oncogenic proteins (MafF, MafG or MafK). Under normal conditions, the BACH1-Maf dimer remains bound to the ARE motif in HMOX1 gene promoter and acts as a repressor of its transcription ^[34]. However, BACH1 has a heme-binding region, which upon interaction with heme molecules present in the nucleus, promotes dissociation of BACH1 from the Maf protein and from the ARE motif in the HO-1 gene promoter. This event is followed by translocation of BACH1 molecule to the cytoplasm where it undergoes ubiquitination and further degradation by the proteasome ^[35]. With BACH1 now displaced from the nucleus, Maf forms a dimer with the Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) transcription factor, which then binds to the same ARE region and induces HO-1 gene transcription ^{[36][37]}.

In order to induce HO-1 expression, NRF2 must be activated simultaneously with BACH1 inactivation. This process is driven by electrophilic and oxidative stresses, which occur for example when heightened production of reactive oxygen species (ROS) is detected ^{[38][39]}. During resting conditions, NRF2 is found in the cytoplasm, associated with the protein Kelch-like ECH-Associated Protein 1 (KEAP1), which promotes NRF2 ubiquitination, resulting in proteasomal degradation of the transcription factor ^[40]. Upon induction of electrophilic and oxidative stresses, the resulting reactive species will cause modifications in specific cysteine residues present on KEAP1, resulting in inhibition of NRF2 ubiquitination. The transcription factor is then released from KEAP1 and translocated to the nucleus where it will dimerize with small Maf proteins to induce HO-1 gene transcription as described above ^{[41][42][43]}.

As already mentioned, oxidative stress is a major inducer of HO-1 expression and is a process closely linked with inflammation ^{[44][45]}. However, a number of different signaling pathways and transcription factors triggered by inflammatory mediators, danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) have also been reported to trigger HMOX1 transcription ^{[46][47]}. Mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), tyrosine kinases and protein kinases (PK) A, B, C and G signaling cascades are commonly activated in response to the above mentioned stimuli and are all involved in the induction of HO-1 expression ^{[48][49][50]}. For example, PKC can directly phosphorylate a serine residue located at position 40 on the NRF2 protein, which results in its disruption from KEAP1 thus promoting NRF2 translocation to the nucleus ^[51]. It has also been reported that NRF2 can be directly phosphorylated at several serine and threonine sites by different MAPKs in vivo. Of note, in that latter case, no effects on NRF2-KEAP1 interaction were observed ^[52]. Indeed, a number of additional studies have confirmed that MAPK activities can induce NRF2 activation in response to different stimuli ^{[53][54][55][56]}, however, they leave open the possibility that the effect of these enzymes on NRF2 signaling may be indirect.

It is important to note that there are regions in the HO-1 gene promoter that serve as binding sites for other transcription factors apart from NRF2, whose expression can be induced as a result of activation of the same signaling cascades mentioned above, such as heat-shock factors (HSFs), activator protein-1 (AP-1), nuclear factor-kappa B (NF κ B) and hypoxia-induced factor 1 α (HIF1 α) ^[57]. These alternative pathways are briefly described below.

In rats, two genomic motifs known as heat shock elements (HSEs) are present in the HO-1 gene promoter that serve as binding sites for HSF and have been shown to play a role in the induction of HO-1 expression in response to hyperthermia ^[58]. In mouse fibroblasts, deletion of the HSF-1 gene results in marked reduction of HO-1 expression in response to heat shock injury ^[59]. However, the mechanisms involved in HO-1 induction by the interaction of HSF with HSEs in the HO-1 gene promoter vary among species. For example, HSEs identified in the rat HMOX1 promoter are inactive in humans and mice , and therefore, further studies are needed to fully elucidate this putative pathway for HO-1 induction.

The transcription factor AP-1 actually encompasses a family of structurally and functionally related transcription factors composed of dimers made up of members of the Jun (c-Jun, JunB and JunD), Fos (c-Fos, FosB, Fra1 and Fra2), ATF (Atf2, Atf3, Atf4, Atf5, Atf6B, Atf7, BATF, BATF2, BATF3, JDP1 and JDP2) and Maf (c-Maf, MafA, MafB, MafF, MafG and MafK Nrl) DNA-binding protein families ^[60]. Functional AP-1 binding sites have been identified in promoter regions of mouse, rat and human HO-1 genes ^{[61][62][63]} and studies have demonstrated a role for AP-1 in the induction of HO-1 expression in cells from mice, rats and humans ^{[64][65][66]}. However, the mechanisms through which AP-1 regulates the induction of HO-1 expression are complex and may involve a cooperative interaction between AP-1 subunits and different transcription factors ^{[66][67][68]}, including NRF2 ^[69].

NF κ B, similar to AP-1, is a generic term that denotes transcription factors formed by the homo or heterodimerization of components of the Rel family of proteins, namely RelA (p65), RelB, c-Rel, p52 and p50 ^[70]. During resting conditions, NF κ B is found in the cytoplasm in an inactive state bound to the Inhibitor of NF κ B molecule (I- κ B). Upon cell stimulation, the transcription factor subunits are released from I- κ B (which is phosphorylated by the kinase IKK—I- κ B kinase—and further degraded by the proteasome) and translocated to the nucleus, where they bind to promoter regions of specific genes and induce their transcription ^[71]. Functional binding sites for NF κ B were identified in the promoter regions of the HO-1 gene. These sites were found to be involved in the induction of rat HO-1 expression in response to phorbol myristate acetate (PMA) in vitro ^[72] and also in the NOS2-mediated upregulation of HO-1 expression in mouse cardiac tissue ^[73].

HIFs are a family of transcription factors whose expression is upregulated in response to low oxygen concentrations. They are composed of a constant subunit (HIF1 β) and one of three variable α subunits (HIF1 α , HIF2 α and HIF3 α), which provide the name for the whole heterodimer. Oxygen is used as a cofactor by the enzyme prolyl hydroxylase (PHD), which initiates a process culminating in ubiquitination and proteasomal degradation of α subunits. As a consequence, under hypoxic conditions, PHD is held inactive resulting in stabilization of α subunits. This process allows these subunits to dimerize with HIF1 β and be translocated to the nucleus to initiate gene transcription ^{[74][75]}. HIF1 α is by far the best studied of these factors and its expression is highly upregulated during inflammation ^[76]. Binding sites for HIF1 α have been identified in the rat HMOX1 gene approximately 9.5 kilobases upstream of the transcription start site and were shown to be responsible for the induction of HO-1 expression in response to hypoxia in rat aortic vascular muscle cells ^[72]. Induction of HO-1 transcription in response to direct binding of HIF1 α to DNA has also been observed in rat renal medullary interstitial cells as well ^[78]. Human cells also upregulate HO-1 in response to HIF1 α , although direct HO-1 induction by HIF1 α binding to the HMOX1 gene was not demonstrated ^[79].

The existence of multiple pathways for triggering and repressing HO-1 transcription (summarized in Figure 1) is consistent with a central role for the enzyme in responding to a wide variety of inflammatory stimuli and within a range of different host cell types.



Figure 1. Molecular mechanisms underlying the regulation of HMOX1 gene transcription. (**A**) In homeostatic conditions, NRF2 is found in the cytosol of cells bound to KEAP1, which promotes ubiquitination of NRF2 that is further degraded in proteasomes. In the nucleus, the transcription factor BACH1 remains bound in association with a small Maf protein to the ARE region in HMOX1 gene promoter repressing its transcription. (**B**) Under stress conditions, binding of heme molecules to BACH1 in the nucleus promotes its displacement from the small Maf protein and ARE motif in the HMOX1 gene promoter, while in the cytosol, ROS induce changes in KEAP1 cysteine residues that promote the release of NRF2 and prevents its ubiquitination and degradation. (**C**) NRF2 is translocated to the nucleus, where it associates to a small Maf protein and binds to the ARE motif in HMOX1 gene promoter inducing its expression, while heme-bound BACH1 is excluded from the nucleus. (**D**) Signaling cascades involved in the induction of HMOX1 gene expression (MAPK, PI3K and PKA, B, C and G—cytosol) and transcription factors to which recognition motifs were identified in the HMOX1 gene or that were shown to induce HO-1 expression (HIF1α, HSF, AP-1 and NFκB—nucleus).

References

- 1. Morse, D.; Choi, A.M. Heme oxygenase-1: From bench to bedside. Am. J. Resp. Crit. Care 2005, 172, 660–670, doi:10.1164/rccm.200404-465SO.
- Tenhunen, R.; Marver, H.S.; Schmid, R. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. Proc. Natl. Acad. Sci. USA 1968, 61, 748–755, doi:10.1073/pnas.61.2.748.
- 3. Maines, M.D.; Ibrahim, N.G.; Kappas, A. Solubilization and partial purification of heme oxygenase from rat liver. J. Biol. Chem. 1977, 252, 5900–5903.
- 4. Maines, M.D.; Trakshel, G.M.; Kutty, R.K. Characterization of two constitutive forms of rat liver microsomal heme oxygenase. Only one molecular species of the enzyme is inducible. J. Biol. Chem. 1986, 261, 411–419.
- 5. Hiwasa, T.; Sakiyama, S. Increase in the synthesis of a Mr 32,000 protein in BALB/c 3T3 cells after treatment with tumor promoters, chemical carcinogens, metal salts, and heat shock. Cancer Res. 1986, 46, 2474–2481.
- Caltabiano, M.M.; Koestler, T.P.; Poste, G.; Greig, R.G. Induction of 32- and 34-kDa stress proteins by sodium arsenite, heavy metals, and thiol-reactive agents. J. Biol. Chem. 1986, 261, 13381–13386.
- Caltabiano, M.M.; Koestler, T.P.; Poste, G.; Greig, R.G. Induction of mammalian stress proteins by a triethylphosphine gold compound used in the therapy of rheumatoid arthritis. Biochem. Biophys. Res. 1986, 138, 1074–1080, doi:10.1016/s0006-291x(86)80391-6.
- 8. Keyse, S.M.; Tyrrell, R.M. Both near ultraviolet radiation and the oxidizing agent hydrogen peroxide induce a 32-kDa stress protein in normal human skin fibroblasts. J. Biol. Chem. 1987, 262, 14821–14825.
- 9. Caltabiano, M.M.; Poste, G.; Greig, R.G. Induction of the 32-kD human stress protein by auranofin and related triethylphosphine gold analogs. Biochem. Pharmacol. 1988, 37, 4089–4093, doi:10.1016/0006-2952(88)90100-1.
- 10. Caltabiano, M.M.; Poste, G.; Greig, R.G. Isolation and immunological characterization of the mammalian 32-/34-kDa stress protein. Exp. Cell Res. 1988, 178, 31–40, doi:10.1016/0014-4827(88)90375-8.

- 11. Taketani, S.; Kohno, H.; Yoshinaga, T.; Tokunaga, R. The human 32-kDa stress protein induced by exposure to arsenite and cadmium ions is heme oxygenase. FEBS Lett. 1989, 245, 173–176, doi:10.1016/0014-5793(89)80215-7.
- 12. Keyse, S.M.; Tyrrell, R.M. Heme oxygenase is the major 32-kDa stress protein induced in human skin fibroblasts by UVA radiation, hydrogen peroxide, and sodium arsenite. Proc. Natl. Acad. Sci. USA 1989, 86, 99–103.
- McCoubrey, W.K., Jr.; Huang, T.J.; Maines, M.D. Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. Eur. J. Biochem. 1997, 247, 725–732, doi:10.1111/j.1432-1033.1997.00725.x.
- Hayashi, S.; Omata, Y.; Sakamoto, H.; Higashimoto, Y.; Hara, T.; Sagara, Y.; Noguchi, M. Characterization of rat heme oxygenase-3 gene. Implication of processed pseudogenes derived from heme oxygenase-2 gene. Gene 2004, 336, 241–250, doi:10.1016/j.gene.2004.04.002.
- 15. Wilks, A. Heme oxygenase: Evolution, structure, and mechanism. Antioxid. Redox Signal. 2002, 4, 603–614, doi:10.1089/15230860260220102.
- 16. Munoz-Sanchez, J.; Chanez-Cardenas, M.E. A review on hemeoxygenase-2: Focus on cellular protection and oxygen response. Oxid. Med. Cell. Longev. 2014, 2014, 604981, doi:10.1155/2014/604981.
- Fleischhacker, A.S.; Gunawan, A.L.; Kochert, B.A.; Liu, L.; Wales, T.E.; Borowy, M.C.; Engen, J.R.; Ragsdale, S.W. The heme-regulatory motifs of heme oxygenase-2 contribute to the transfer of heme to the catalytic site for degradation. J. Biol. Chem. 2020, 295, 5177–5191, doi:10.1074/jbc.RA120.012803.
- 18. Montellano, P.R. The mechanism of heme oxygenase. Curr. Opin. Chem. Biol. 2000, 4, 221–227, doi:10.1016/s1367-5931(99)00079-4.
- 19. Maines, M.D. The heme oxygenase system: A regulator of second messenger gases. Annu. Rev. Pharmacol. Toxicol. 1997, 37, 517–554, doi:10.1146/annurev.pharmtox.37.1.517.
- 20. Maines, M.D. Heme oxygenase: Function, multiplicity, regulatory mechanisms, and clinical applications. FASEB J. 1988, 2, 2557–2568.
- 21. Chung, S.W.; Hall, S.R.; Perrella, M.A. Role of haem oxygenase-1 in microbial host defence. Cell Microbiol. 2009, 11, 199–207, doi:10.1111/j.1462-5822.2008.01261.x.
- 22. Vijayan, V.; Wagener, F.; Immenschuh, S. The macrophage heme-heme oxygenase-1 system and its role in inflammation. Biochem. Pharmacol. 2018, 153, 159–167, doi:10.1016/j.bcp.2018.02.010.
- 23. Contreras, H.; Chim, N.; Credali, A.; Goulding, C.W. Heme uptake in bacterial pathogens. Curr. Opin. Chem. Biol. 2014, 19, 34–41, doi:10.1016/j.cbpa.2013.12.014.
- 24. Bozza, M.T.; Jeney, V. Pro-inflammatory Actions of Heme and Other Hemoglobin-Derived DAMPs. Front. Immunol. 2020, 11, 1323, doi:10.3389/fimmu.2020.01323.
- 25. Waza, A.A.; Hamid, Z.; Ali, S.; Bhat, S.A.; Bhat, M.A. A review on heme oxygenase-1 induction: Is it a necessary evil. Inflamm. Res. 2018, 67, 579–588, doi:10.1007/s00011-018-1151-x.
- 26. Singh, N.; Ahmad, Z.; Baid, N.; Kumar, A. Host heme oxygenase-1: Friend or foe in tackling pathogens? IUBMB Life 2018, 70, 869–880, doi:10.1002/iub.1868.
- 27. Fraser, S.T.; Midwinter, R.G.; Berger, B.S.; Stocker, R. Heme Oxygenase-1: A Critical Link between Iron Metabolism, Erythropoiesis, and Development. Adv. Hematol. 2011, 2011, 473709, doi:10.1155/2011/473709.
- 28. Reedy, C.J.; Gibney, B.R. Heme protein assemblies. Chem. Rev. 2004, 104, 617–649, doi:10.1021/cr0206115.
- 29. Hvidberg, V.; Maniecki, M.B.; Jacobsen, C.; Hojrup, P.; Moller, H.J.; Moestrup, S.K. Identification of the receptor scavenging hemopexin-heme complexes. Blood 2005, 106, 2572–2579, doi:10.1182/blood-2005-03-1185.
- 30. Kristiansen, M.; Graversen, J.H.; Jacobsen, C.; Sonne, O.; Hoffman, H.J.; Law, S.K.; Moestrup, S.K. Identification of the haemoglobin scavenger receptor. Nature 2001, 409, 198–201, doi:10.1038/35051594.
- Rajagopal, A.; Rao, A.U.; Amigo, J.; Tian, M.; Upadhyay, S.K.; Hall, C.; Uhm, S.; Mathew, M.K.; Fleming, M.D.; Paw, B.H.; et al. Haem homeostasis is regulated by the conserved and concerted functions of HRG-1 proteins. Nature 2008, 453, 1127–1131, doi:10.1038/nature06934.
- 32. White, C.; Yuan, X.; Schmidt, P.J.; Bresciani, E.; Samuel, T.K.; Campagna, D.; Hall, C.; Bishop, K.; Calicchio, M.L.; Lapierre, A.; et al. HRG1 is essential for heme transport from the phagolysosome of macrophages during erythrophagocytosis. Cell Metab. 2013, 17, 261–270, doi:10.1016/j.cmet.2013.01.005.
- Tudor, C.; Lerner-Marmarosh, N.; Engelborghs, Y.; Gibbs, P.E.; Maines, M.D. Biliverdin reductase is a transporter of haem into the nucleus and is essential for regulation of HO-1 gene expression by haematin. Biochem. J. 2008, 413, 405–416, doi:10.1042/BJ20080018.

- 34. Zhang, X.; Guo, J.; Wei, X.; Niu, C.; Jia, M.; Li, Q.; Meng, D. Bach1: Function, Regulation, and Involvement in Disease. Oxid. Med. Cell Longev. 2018, 2018, 1347969, doi:10.1155/2018/1347969.
- 35. Zenke-Kawasaki, Y.; Dohi, Y.; Katoh, Y.; Ikura, T.; Ikura, M.; Asahara, T.; Tokunaga, F.; Iwai, K.; Igarashi, K. Heme induces ubiquitination and degradation of the transcription factor Bach1. Mol. Cell Biol. 2007, 27, 6962–6971, doi:10.1128/MCB.02415-06.
- Igarashi, K.; Kataoka, K.; Itoh, K.; Hayashi, N.; Nishizawa, M.; Yamamoto, M. Regulation of transcription by dimerization of erythroid factor NF-E2 p45 with small Maf proteins. Nature 1994, 367, 568–572, doi:10.1038/367568a0.
- 37. Reichard, J.F.; Motz, G.T.; Puga, A. Heme oxygenase-1 induction by NRF2 requires inactivation of the transcriptional repressor BACH1. Nucleic Acids Res. 2007, 35, 7074–7086, doi:10.1093/nar/gkm638.
- Itoh, K.; Wakabayashi, N.; Katoh, Y.; Ishii, T.; O'Connor, T.; Yamamoto, M. Keap1 regulates both cytoplasmic-nuclear shuttling and degradation of Nrf2 in response to electrophiles. Genes Cells 2003, 8, 379–391, doi:10.1046/j.1365-2443.2003.00640.x.
- Kobayashi, A.; Kang, M.I.; Watai, Y.; Tong, K.I.; Shibata, T.; Uchida, K.; Yamamoto, M. Oxidative and electrophilic stresses activate Nrf2 through inhibition of ubiquitination activity of Keap1. Mol. Cell Biol. 2006, 26, 221–229, doi:10.1128/MCB.26.1.221-229.2006.
- 40. Baird, L.; Dinkova-Kostova, A.T. The cytoprotective role of the Keap1-Nrf2 pathway. Arch. Toxicol. 2011, 85, 241–272, doi:10.1007/s00204-011-0674-5.
- 41. Yamamoto, M.; Kensler, T.W.; Motohashi, H. The KEAP1-NRF2 System: A Thiol-Based Sensor-Effector Apparatus for Maintaining Redox Homeostasis. Physiol. Rev. 2018, 98, 1169–1203, doi:10.1152/physrev.00023.2017.
- 42. Suzuki, T.; Yamamoto, M. Molecular basis of the Keap1-Nrf2 system. Free Radic. Biol. Med. 2015, 88, 93–100, doi:10.1016/j.freeradbiomed.2015.06.006.
- 43. Alam, J.; Stewart, D.; Touchard, C.; Boinapally, S.; Choi, A.M.; Cook, J.L. Nrf2, a Cap'n'Collar transcription factor, regulates induction of the heme oxygenase-1 gene. J. Biol. Chem. 1999, 274, 26071–26078.
- 44. Hajjar, D.P.; Gotto, A.M., Jr. Biological relevance of inflammation and oxidative stress in the pathogenesis of arterial diseases. Am. J. Pathol. 2013, 182, 1474–1481, doi:10.1016/j.ajpath.2013.01.010.
- 45. Binder, C.J.; Papac-Milicevic, N.; Witztum, J.L. Innate sensing of oxidation-specific epitopes in health and disease. Nat. Rev. Immunol. 2016, 16, 485–497, doi:10.1038/nri.2016.63.
- 46. Paine, A.; Eiz-Vesper, B.; Blasczyk, R.; Immenschuh, S. Signaling to heme oxygenase-1 and its anti-inflammatory therapeutic potential. Biochem. Pharmacol. 2010, 80, 1895–1903, doi:10.1016/j.bcp.2010.07.014.
- 47. Hull, T.D.; Agarwal, A.; George, J.F. The mononuclear phagocyte system in homeostasis and disease: A role for heme oxygenase-1. Antioxid. Redox Signal. 2014, 20, 1770–1788, doi:10.1089/ars.2013.5673.
- 48. Alam, J.; Cook, J.L. How many transcription factors does it take to turn on the heme oxygenase-1 gene? Am. J. Respir. Cell. Mol. Biol. 2007, 36, 166–174, doi:10.1165/rcmb.2006-0340TR.
- 49. Ryter, S.W.; Alam, J.; Choi, A.M. Heme oxygenase-1/carbon monoxide: From basic science to therapeutic applications. Physiol. Rev. 2006, 86, 583–650, doi:10.1152/physrev.00011.2005.
- 50. Newton, K.; Dixit, V.M. Signaling in innate immunity and inflammation. Cold Spring Harb. Perspect. Biol. 2012, 4, a006049, doi:10.1101/cshperspect.a006049.
- 51. Bloom, D.A.; Jaiswal, A.K. Phosphorylation of Nrf2 at Ser40 by protein kinase C in response to antioxidants leads to the release of Nrf2 from INrf2, but is not required for Nrf2 stabilization/accumulation in the nucleus and transcriptional activation of antioxidant response element-mediated NAD(P)H:quinone oxidoreductase-1 gene expression. J. Biol. Chem. 2003, 278, 44675–44682, doi:10.1074/jbc.M307633200.
- 52. Sun, Z.; Huang, Z.; Zhang, D.D. Phosphorylation of Nrf2 at multiple sites by MAP kinases has a limited contribution in modulating the Nrf2-dependent antioxidant response. PLoS ONE 2009, 4, e6588, doi:10.1371/journal.pone.0006588.
- Papaiahgari, S.; Kleeberger, S.R.; Cho, H.Y.; Kalvakolanu, D.V.; Reddy, S.P. NADPH oxidase and ERK signaling regulates hyperoxia-induced Nrf2-ARE transcriptional response in pulmonary epithelial cells. J. Biol. Chem. 2004, 279, 42302–42312, doi:10.1074/jbc.M408275200.
- 54. Pae, H.O.; Oh, G.S.; Jeong, S.O.; Jeong, G.S.; Lee, B.S.; Choi, B.M.; Lee, H.S.; Chung, H.T. 1,2,3,4,6-penta-O-galloylbeta-D-glucose up-regulates heme oxygenase-1 expression by stimulating Nrf2 nuclear translocation in an extracellular signal-regulated kinase-dependent manner in HepG2 cells. World J. Gastroenterol. 2006, 12, 214–221, doi:10.3748/wjg.v12.i2.214.
- 55. Xu, C.; Yuan, X.; Pan, Z.; Shen, G.; Kim, J.H.; Yu, S.; Khor, T.O.; Li, W.; Ma, J.; Kong, A.N. Mechanism of action of isothiocyanates: The induction of ARE-regulated genes is associated with activation of ERK and JNK and the

phosphorylation and nuclear translocation of Nrf2. Mol. Cancer Ther. 2006, 5, 1918–1926, doi:10.1158/1535-7163.MCT-05-0497.

- Manandhar, S.; Cho, J.M.; Kim, J.A.; Kensler, T.W.; Kwak, M.K. Induction of Nrf2-regulated genes by 3H-1, 2-dithiole-3thione through the ERK signaling pathway in murine keratinocytes. Eur. J. Pharmacol. 2007, 577, 17–27, doi:10.1016/j.ejphar.2007.08.018.
- Medina, M.V.; Sapochnik, D.; Garcia Sola, M.; Coso, O. Regulation of the Expression of Heme Oxygenase-1: Signal Transduction, Gene Promoter Activation, and Beyond. Antioxid. Redox Signal. 2020, 32, 1033–1044, doi:10.1089/ars.2019.7991.
- 58. Okinaga, S.; Shibahara, S. Identification of a nuclear protein that constitutively recognizes the sequence containing a heat-shock element. Its binding properties and possible function modulating heat-shock induction of the rat heme oxygenase gene. Eur. J. Biochem. 1993, 212, 167–175, doi:10.1111/j.1432-1033.1993.tb17647.x.
- 59. Inouye, S.; Hatori, Y.; Kubo, T.; Saito, S.; Kitamura, H.; Akagi, R. NRF2 and HSF1 coordinately regulate heme oxygenase-1 expression. Biochem. Biophys. Res. 2018, 506, 7–11, doi:10.1016/j.bbrc.2018.10.030.
- 60. Bejjani, F.; Evanno, E.; Zibara, K.; Piechaczyk, M.; Jariel-Encontre, I. The AP-1 transcriptional complex: Local switch or remote command? Biochim. Biophys. Acta Rev. Cancer 2019, 1872, 11–23, doi:10.1016/j.bbcan.2019.04.003.
- 61. Alam, J.; Den, Z. Distal AP-1 binding sites mediate basal level enhancement and TPA induction of the mouse heme oxygenase-1 gene. J. Biol. Chem. 1992, 267, 21894–21900.
- 62. Immenschuh, S.; Hinke, V.; Ohlmann, A.; Gifhorn-Katz, S.; Katz, N.; Jungermann, K.; Kietzmann, T. Transcriptional activation of the haem oxygenase-1 gene by cGMP via a cAMP response element/activator protein-1 element in primary cultures of rat hepatocytes. Biochem. J. 1998, 334 Pt 1, 141–146, doi:10.1042/bj3340141.
- Hock, T.D.; Liby, K.; Wright, M.M.; McConnell, S.; Schorpp-Kistner, M.; Ryan, T.M.; Agarwal, A. JunB and JunD regulate human heme oxygenase-1 gene expression in renal epithelial cells. J. Biol. Chem. 2007, 282, 6875–6886, doi:10.1074/jbc.M608456200.
- Camhi, S.L.; Alam, J.; Otterbein, L.; Sylvester, S.L.; Choi, A.M. Induction of heme oxygenase-1 gene expression by lipopolysaccharide is mediated by AP-1 activation. Am. J. Respir. Cell Mol. Biol. 1995, 13, 387–398, doi:10.1165/ajrcmb.13.4.7546768.
- Gong, P.; Stewart, D.; Hu, B.; Vinson, C.; Alam, J. Multiple basic-leucine zipper proteins regulate induction of the mouse heme oxygenase-1 gene by arsenite. Arch. Biochem. Biophys. 2002, 405, 265–274, doi:10.1016/s0003-9861(02)00404-6.
- Wright, M.M.; Kim, J.; Hock, T.D.; Leitinger, N.; Freeman, B.A.; Agarwal, A. Human haem oxygenase-1 induction by nitro-linoleic acid is mediated by cAMP, AP-1 and E-box response element interactions. Biochem. J. 2009, 422, 353– 361, doi:10.1042/BJ20090339.
- Samoylenko, A.; Dimova, E.Y.; Horbach, T.; Teplyuk, N.; Immenschuh, S.; Kietzmann, T. Opposite expression of the antioxidant heme oxygenase-1 in primary cells and tumor cells: Regulation by interaction of USF-2 and Fra-1. Antioxid. Redox Signal. 2008, 10, 1163–1174, doi:10.1089/ars.2007.1968.
- Deshane, J.; Kim, J.; Bolisetty, S.; Hock, T.D.; Hill-Kapturczak, N.; Agarwal, A. Sp1 regulates chromatin looping between an intronic enhancer and distal promoter of the human heme oxygenase-1 gene in renal cells. J. Biol. Chem. 2010, 285, 16476–16486, doi:10.1074/jbc.M109.058586.
- 69. Lu, C.Y.; Yang, Y.C.; Li, C.C.; Liu, K.L.; Lii, C.K.; Chen, H.W. Andrographolide inhibits TNFalpha-induced ICAM-1 expression via suppression of NADPH oxidase activation and induction of HO-1 and GCLM expression through the PI3K/Akt/Nrf2 and PI3K/Akt/AP-1 pathways in human endothelial cells. Biochem. Pharmacol. 2014, 91, 40–50, doi:10.1016/j.bcp.2014.06.024.
- Liu, T.; Zhang, L.; Joo, D.; Sun, S.C. NF-kappaB signaling in inflammation. Signal. Transduct. Target. Ther. 2017, 2, 1– 9, doi:10.1038/sigtrans.2017.23.
- Mitchell, S.; Vargas, J.; Hoffmann, A. Signaling via the NFkappaB system. Wiley Interdiscip. Rev. Syst. Biol. Med. 2016, 8, 227–241, doi:10.1002/wsbm.1331.
- 72. Naidu, S.; Wijayanti, N.; Santoso, S.; Kietzmann, T.; Immenschuh, S. An atypical NF-kappa B-regulated pathway mediates phorbol ester-dependent heme oxygenase-1 gene activation in monocytes. J. Immunol. 2008, 181, 4113–4123, doi:10.4049/jimmunol.181.6.4113.
- 73. Li, Q.; Guo, Y.; Ou, Q.; Cui, C.; Wu, W.J.; Tan, W.; Zhu, X.; Lanceta, L.B.; Sanganalmath, S.K.; Dawn, B.; et al. Gene transfer of inducible nitric oxide synthase affords cardioprotection by upregulating heme oxygenase-1 via a nuclear factor-{kappa}B-dependent pathway. Circulation 2009, 120, 1222–1230, doi:10.1161/CIRCULATIONAHA.108.778688.

- Peyssonnaux, C.; Zinkernagel, A.S.; Schuepbach, R.A.; Rankin, E.; Vaulont, S.; Haase, V.H.; Nizet, V.; Johnson, R.S. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). J. Clin. Investig. 2007, 117, 1926– 1932, doi:10.1172/JCI31370.
- 75. Palazon, A.; Goldrath, A.W.; Nizet, V.; Johnson, R.S. HIF transcription factors, inflammation, and immunity. Immunity 2014, 41, 518–528, doi:10.1016/j.immuni.2014.09.008.
- 76. Lin, N.; Simon, M.C. Hypoxia-inducible factors: Key regulators of myeloid cells during inflammation. J. Clin. Investig. 2016, 126, 3661–3671, doi:10.1172/JCI84426.
- 77. Lee, P.J.; Jiang, B.H.; Chin, B.Y.; Iyer, N.V.; Alam, J.; Semenza, G.L.; Choi, A.M. Hypoxia-inducible factor-1 mediates transcriptional activation of the heme oxygenase-1 gene in response to hypoxia. J. Biol. Chem. 1997, 272, 5375–5381.
- 78. Yang, Z.Z.; Zou, A.P. Transcriptional regulation of heme oxygenases by HIF-1alpha in renal medullary interstitial cells. Am. J. Physiol. Renal. Physiol. 2001, 281, F900–F908, doi:10.1152/ajprenal.2001.281.5.F900.
- 79. Ockaili, R.; Natarajan, R.; Salloum, F.; Fisher, B.J.; Jones, D.; Fowler, A.A., 3rd; Kukreja, R.C. HIF-1 activation attenuates postischemic myocardial injury: Role for heme oxygenase-1 in modulating microvascular chemokine generation. Am. J. Physiol. Heart Circ. Physiol. 2005, 289, H542–H548, doi:10.1152/ajpheart.00089.2005.

Retrieved from https://encyclopedia.pub/entry/history/show/10775