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Mini Review

Heme oxygenase-1 comes back to endoplasmic reticulum

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ABSTRACT

Originally identified as a rate-limiting enzyme for heme catabolism, heme oxygenase-1 (HO-1) has expanded its roles in anti-inflammation, anti-apoptosis and anti-proliferation for the last decade. Regulation of protein activity by location is well appreciated. Even though multiple compartmentalization of HO-1 has been documented, the functional implication of this enzyme at these subcellular organelles is only partially elucidated. In this review we discuss the endoplasmic reticulum (ER)-residing HO-1 and its cytoprotective activity against ER stress.

1. Introduction

Heme oxygenase-1 (HO-1), a ubiquitous stress-inducible protein, plays a major metabolic function in heme catabolism with accessory proteins. HO-1 enzymatic complex cleaves heme to form biliverdin-IXα, carbon monoxide (CO), and iron. By itself or its enzymatic products, HO-1 functions in tissue homeostasis *via* suppressing oxidative stress and maintaining cellular integrity [1,2].

Due to the high affinity of CO with heme proteins and intrinsic antioxidative property of biliverdin (BV)/bilirubin (BR), the biological functions of HO-1 have been focused on the role of the by-products. Genetic experiments reveal the physiological significance of HO-1, namely anti-apoptotic, anti-proliferative effect and immunoregulatory functions [3].

Accumulated findings showed that HO-1 compartmentalizes to the endoplasmic reticulum (ER), plasma membrane, mitochondria and nucleus forced us to consider the *nexus* of location and protein functions [4–7]. Location of a protein at specific compartments is known to guarantee its appropriate metabolic functions in eukaryotic cells [8,9]. Although HO-1 has been known to reside spatially at the ER, the enzyme now functionally comes back to the organelle for protecting cells or organisms against ER-mediated stresses. In this review we discuss the structural features of HO-1 for its full activity and complex formation with accessory proteins especially in the ER and its cytoprotective activity against ER stress.

2. HO-1 expression and subcellular compartmentalization

Gene transcription for HO-1 (*Hmox1*) is inducible by a broad spectrum of stimuli. Such agents include a large number of pharmacological agents as well as a variety of circumstances, such as heat shock and other forms of extracellular and intracellular stresses [1,2]. A number of signaling molecules and transcription factors have been indentified to be involved in the regulation of HO-1 expression [1]. These molecules and factors include mitogen-activated protein kinases (MAPKs), nuclear factor E2-related factor 2 (Nrf2), protein kinase C, protein kinase A, phosphatidyl inositol 3-kinase, activator protein-1, nuclear factor-κB, cyclic adenosine monophosphate-responsive element-binding protein, and activating transcription factor 2 [1]. Among which, contribution of MAPKs and Nrf2 in the transcriptional regulation of HO-1 in diverse cell types is well appreciated.

Conventionally HO-1 is known to be localized to the ER, anchored by a single transmembrane spanning region at the very carboxy-terminal end. To maximize and complete the enzymatic function for heme degradation, HO-1 requires additional enzymes, namely NADPH: cytochrome p450 reductase (CPR) and NAD(P)H: biliverdin reductase (BVR). The multi-enzyme complex may fulfill the heme-metabolizing capacity in eukaryotic cells. Interestingly, however, a subcellular fractionation experiment reveals that microsomal fraction (mainly ER) of rat liver do not have BVR as assessed by Western blotting [8]. The observation evokes questions regarding the composition of HO-1 enzyme complex and their metabolic functions. We also speculated the location of the multi-enzyme complex at other organelles besides ER since dual partitioning of metabolic pathways is evolutionary common in

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eukaryotic cells [9]. We and others have demonstrated diverse localization of HO-1 and its accessory enzymes to plasma membrane, mitochondria and nucleus (Fig. 1) evidenced by biochemical and imaging techniques.

Given the inducibility of HO-1 against a variety of cellular stresses, the distribution and trafficking of the enzyme after *de novo* synthesis to various subcellular organelles needs to be investigated. Sequence analysis of HO-1 protein predicts its possible compartmentalization to ER, mitochondria, nuclei and cytosol (protein WoLFPSORT prediction) as well [10]. However, the "induced targeting" of HO-1 and its functional significance in a specific organelle is partially explored.

Recent study carried out by Huber et al. suggests that human HO-1 might be degraded if it lacks the C-terminal 20 amino acids of transmembrane segment (TMS). Further the full length HO-1 renders maximum catalytic activity compared with soluble cleaved form [11]. Through this TMS, HO-1 seems to transiently form multi-enzyme complexes with CPR and BVR for the completion of heme degradation. More recently, Hwang et al. suggested that HO-1 assembles and forms dimer/oligomers in the ER *via* TMS–TMS interaction. Without the interaction between TMS (amino acids 266–285), HO-1 exit the membrane anchoring and is subjected to be degraded by an ubiquitin–proteasome pathway [12,13]. A transcriptional role of HO-1 without enzymatic activity seems to be derived from the cleaved form of the protein. Overall, the molecular or structural features of induced HO-1 in several subcellular organelles are uncovered questions.

3. Function of HO-1/CO system

A number of studies have demonstrated that HO-1 can confer protective (*i.e.*, anti-inflammatory, anti-apoptotic, anti-proliferative) effects in various experimental models [1]. The underlying mechanisms, however, have not been completely elucidated. Heme is an essential prosthetic group of various enzymes in biological system, but it is inherently dangerous when released from intracellular heme-containing proteins. Free heme can cause cellular injury through oxidative stress by the generation of reactive oxygen species (ROS) [1]. Thus, the removal of the free heme by HO-1 appears to be a primary defense barrier in tissue protection; however, recent evidence suggests that by-products of HO activity (*i.e.,* CO, ferrous iron, and BV/BR), alone or in concert, mediate the protective effects of HO-1 [1]. Direct interaction of HO-1 with signaling molecules or indirect cytoprotective effect of HO-1 by the enzymatic byproducts at specific organelles is anticipated. It is of note that caveolin-1 interacting with death receptor or ROS generating NADPH oxidase complex at the plasma membrane directly binds to the induced HO-1 in endothelial cells (ECs) [14,15]. A similar molecular event might occur in other intracellular compartments such as mitochondria or ER under stressful conditions [6].

4. Endoplasmic reticulum stress and unfolded protein response

Cells must adjust their ER-protein folding capacity according to their environment and physiological context. Those processes that prevent accumulation of unfolded proteins in the ER lumen are highly regulated by an intracellular signaling pathway known as the unfolded protein responses (UPR) [16]. There are a variety of insults that disrupt protein folding in the ER lumen and then activate the UPR. Those include changes in intralumenal calcium, altered glycosylation, nutrient deprivation, pathogen infection, expression of folding-defective proteins, changes in redox status, and adverse metabolic conditions [16]. From these environmental stresses, the ER tries to restore cellular homeostasis by the activation of the UPR such as expansion of ER size, enhancement of folding capacity, reduction in protein synthesis through transcriptional

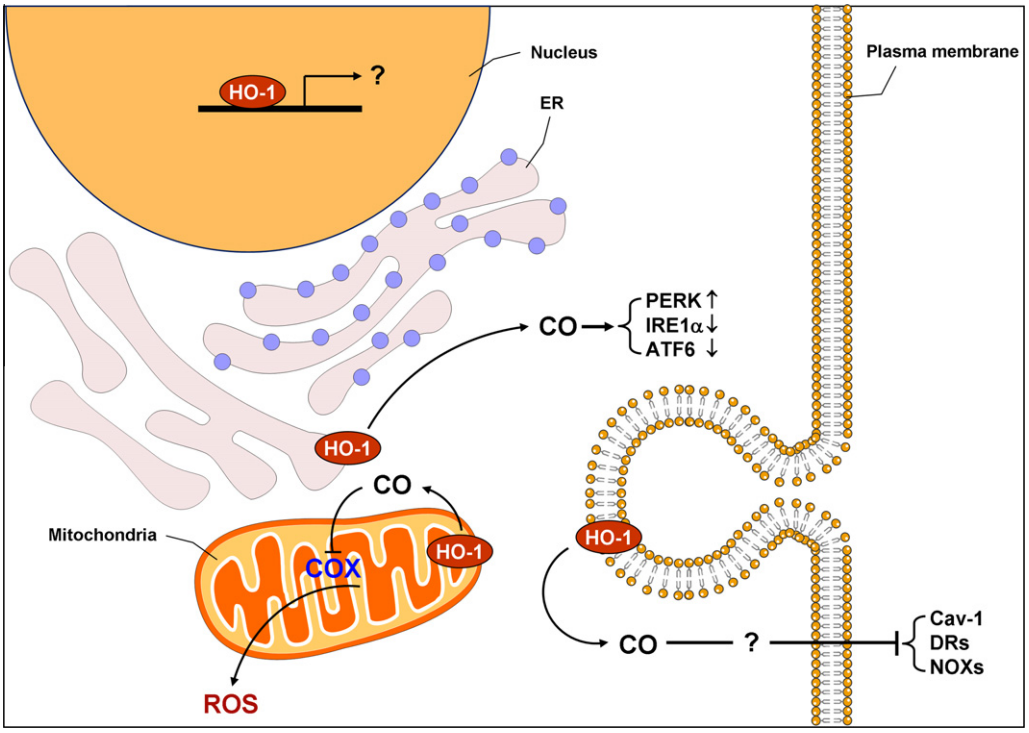

Fig. 1. Diagram for 'induced' HO-1 compartmentalization in intracellular organelles. It has been reported that exogenous and possibly endogenous CO inhibits cytochrome c oxidase (COX) in the mitochondria and generates mild ROS [35]. Reported function of HO-1/CO at specific compartmentalization is depicted. In brief, a direct association of HO-1 with caveolin-1 has been reported at plasma membrane. CO may participate in the control of caveolin-1 binding partners, such as death receptors (DRs) and NADPH oxidase (NOXs). ER-resident HO-1 and its byproduct CO seems to attenuate ER-stress mediated cellular damage by activation of PERK signaling while suppressing IRE1α and ATF6 pathways. A transcriptional role of HO-1 has been suggested.

or translational control, and increase in clearance of unfolded or misfolded proteins [16,17]. When these mechanisms fail to restore ER homeostasis, numerous cell death signaling pathways are activated [18].

The UPR is signaled through activation of three-ER transmembrane localized protein sensors: the protein kinases IRE1α (inositol-requiring 1α), PERK (double-stranded RNA-dependent protein kinase (PKR)-like ER kinase), and the transcription factor ATF6 (activating transcription factor 6) [16,17]. It is proposed that accumulation of unfolded proteins in the ER lumen promotes BiP dissociation from IRE1α, PERK, and ATF6. BiP release from IRE1α and PERK permits their homodimerization, trans-autophosphorylation, and activation [16,17]. IRE1α activation elicits an endoribonuclease function that induces non-conventional splicing of *Xbp1* mRNA. Splicing of *Xbp1* mRNA, the only known splicing substrate of IRE1α, alters the translation reading frame to produce a highly active bZiP transcription factor (XBP1s) [16,17] that activates a wide spectrum of secretory pathway genes encoding proteins involved in protein folding, translocation of nascent polypeptides, ER-Golgi translocation, ER-associated protein degradation (ERAD) genes, and genes remodeling ER and Golgi structure to restore ER homeostasis and maintain ER quality control in stressed cells [16,17]. Upon release from BiP, ATF6 traffics to the Golgi complex where it is cleaved by the processing enzymes (site-1 protease, S1P and site-2 protease, S2P) to produce a mature transcription factor (N-terminal domain of ATF6). The transcription factor induces a variety of gene for ER protein folding (such as BiP and GRP94), ER-associated protein degradation (such as Derlin-3, Herp and EDEM1) and expansion of ER membrane [16,17,19]. By dissociation of BiP, activated PERK phosphorylates the alpha subunit of the translation initiation factor 2 (eIF2α) leading to rapid and transient inhibition of general protein synthesis [16], thereby globally reducing the load of newly synthesized proteins in the lumen of the ER. Phosphorylation of eIF2α by PERK is not only responsible for mRNA translation attenuation, but also plays a key role in transcriptional control [16]. Phosphorylation of eIF2α selectively activates several mRNA (*Gddd34*, *Chop*, *Atf5*, and *Cat1*) including the bZiP transcription factor *Atf4* mRNA [16]. It is proposed that ATF4 promotes cell survival by inducing expression of genes for amino acid biosynthesis and transport, antioxidative stress responses, and protein folding and secretion [20]. Thus, activation of each arm of the UPR initiates adaptive mechanisms to relieve the protein folding defect in the ER, thereby maintaining cellular function and avoiding apoptosis during chronic stress.

However, if ER stress is severe and chronic, the UPR-mediated efforts to correct the protein-folding defect fail and the apoptotic pathway is preferentially activated over time [18]. ER stress leads to several redundant mitochondria-dependent and independent apoptotic pathways [18]. Activated IREα interacts with the tumor necrosis factor receptor associated factor 2 (TRAF2) and apoptosis signal-regulating kinase1 (ASK1) [16,18]. This heterotrimeric complex promotes apoptosis through JNK phosphorylation and activation of the proapoptotic protein BIM, while inhibiting the antiapoptotic protein BCL-2 [18]. Furthermore, several proapototic or antiapototic proteins (*i.e.*, BAX/BAK, ASK1-interacting protein 1 [AIP1], BAX inhibitor-1 [BI-1], and PTP-1B) interact with IRE1α, regulating its activation status [18]. Recent studies reported that under irremediably strong ER stress, activation of IRE1α accompanies the decay of many ER-localized mRNAs encoding secretory cargo proteins, and secretory pathway-resident proteins that promote folding of cargo including *Xbp1* mRNA [21]. It seems that continued decay of these mRNAs under unmitigated ER stress depletes crucial cell surface signaling proteins and triggers a switch into apoptosis (Fig. 2).

During periods of ER stress, the selective translation of *Atf4* mRNA produces a factor that binds to the amino acid response element (AARE) in target genes such as *Atf3*, *Chop*/*Gadd153* and *Gadd34*/*D116*/*Ppp1r15a* [20]. Recent studies indicate that induction of CHOP, a member of C/EBP family of bZIP transcription factor that forms heterodimers with other C/EBP family members, is essential

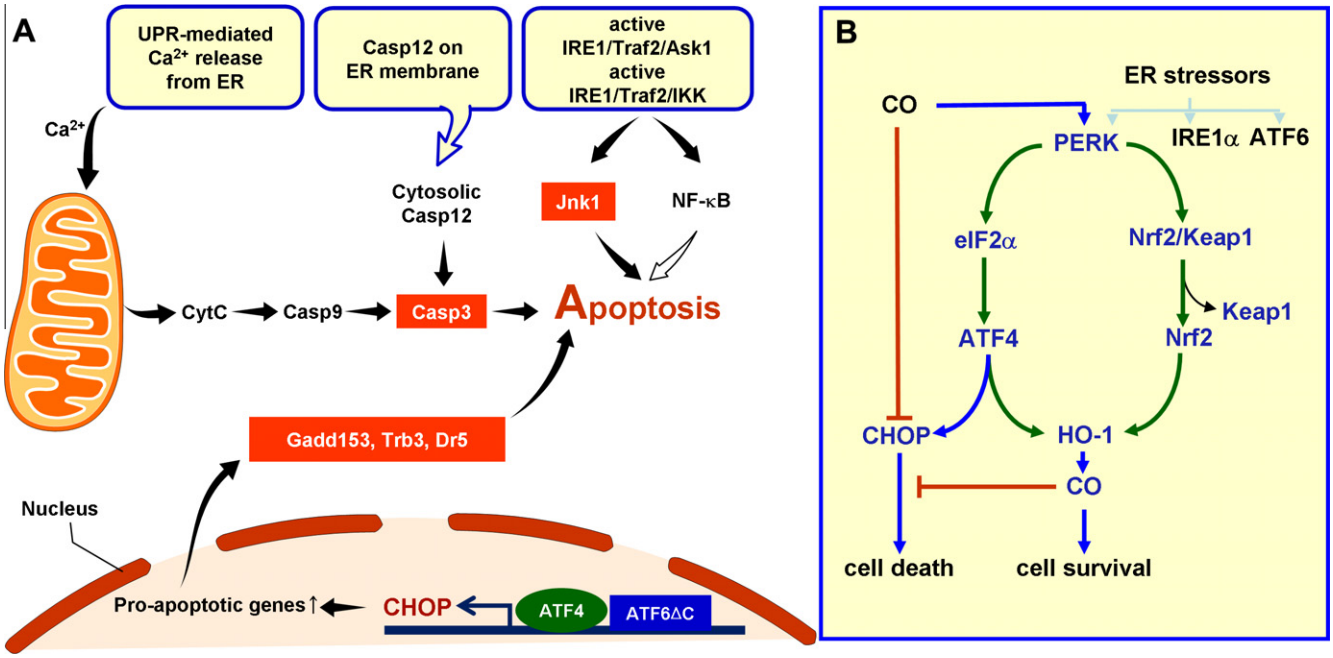

Fig. 2. ER-stress mediated death and survival pathways. (A) Different pathways which lead to cellular apoptosis triggered by ER-stress are illustrated. Calpain-dependent activation of caspase-12, followed by caspase-3 activation leads to cellular apoptosis [36]. Intrinsic death pathway (involving mitochondria) and JNK1-mediated cascade of death signaling contributes ER-stress-mediated cellular damage. A direct transcriptional control of Gadd153, Trb3, and DR 5 by ATF-CHOP is well defined. (B) The UPR responses comprise three branches, IRE1α, ATF6 and PERK pathways. Anti-apoptotic effects of CO *via* the activation of PERK-Nrf2-HO-1 axis and PERK-eIF2α-ATF4 pathways results in CHOP downregulation.

for the apoptotic response to chronic protein misfolding in the ER [18]. Overexpression of CHOP represses transcription of the antiapoptotic protein BCL-2, which leads to enhanced oxidant injury and increased apoptosis [18] and also increases expression of the proapoptotic genes such as growth arrest and DNA damage 34 (GADD34), ER oxidoreductase 1 α (ERO1α), carbonic anhydrase VI, tribbles-related protein3 (Trb3) and death receptor5 (Dr5) [18]. A regulatory subunit of protein phosphatase 1 (PP1), GADD34 dephosphorylates eIF2α to restore translation attenuation [22]. Therefore, expression of GADD34 by CHOP promotes ER client protein biosynthesis in stressed cells, and it causes to accumulate high molecular weight (HMW) detergent-resistant ER complexes in the ER. In addition, ER stress induced ERO1α hyperoxidizes the ER and produces ROS in oxidative protein folding pathway, and it further increase abnormal HMW protein complexes in the stressed ER [23]. Thus, CHOP may induce cell death by promoting protein synthesis and generation of ROS in the stressed ER. Furthermore, recent studies suggest that CHOP is also involved in Ca^{2+}-mediated mitochondria-dependent and -independent apoptotic pathways through activation of calcium/calmodulin-dependent protein kinase IIγ (CaMKIIγ) [24]. The ER Ca^{2+} released through oxidized inositol triposphate receptor (IP3R) activates three apoptotic pathways [25]. First, the activated CaMKIIγ mediates JNK (through mitogen-activated protein kinase kinase4 (MKK4) activation)-mediated Fas induction. Second, activated CaMKIIγ promotes mitochondrial calcium uptake, thereby activates mitochondrial apoptosis and third, CaMKIIγ mediates activation of STAT1, a proapoptotic signal transducer. Thus, the PERK-mediated cell death pathway is mainly attributed to the transcriptional activity of CHOP (Fig. 2).

5. Role of HO-1/CO system in ER stress

The PERK pathway of the UPR can also activate an antioxidant program by preferentially translating mRNA encoding ATF4 and by phosphorylation of Nrf2 [26]. Nrf2 activation has been implicated in the promotion of cell survival following ER stress [26]. In addition, Liu et al. [27] have examined whether ER stress could regulate HO-1 expression in vascular smooth muscle cells (VSMCs). According to the study, HO-1 expression is induced by a diverse set of conditions that cause ER stress, including inhibition of protein transport, calcium depletion, homocysteine exposure, and aberrant protein accumulation. Thus, the activation of Nrf2 appears to be involved in HO-1 expression by ER stress [26,27]. Furthermore, Kim et al. [28] have demonstrated that CO induces HO-1 expression in human ECs by activating Nrf2 through PERK phosphorylation. Thus, it is most likely that ER stress may induce HO-1 expression through PERK-dependent Nrf2 activation.

With regards to the potential physiological importance of HO-1 in mediating cellular homeostasis, the functional role of HO-1 during ER stress has been investigated by Liu et al. [27]. Homocysteine, an ER stress inducer, induced apoptosis in VSMCs. Induction of apoptosis by homocysteine was further increased in the presence of the HO inhibitors, zinc protoporphyrin-IX or tin protoporphyrin-IX, suggesting that the induction of HO-1 by ER stress may function in an autocrine manner to inhibit apoptosis. Interestingly, the cytoprotection afforded by HO-1 was mimicked by CO, but not by the other HO-1 products, indicating that the anti-apoptotic effect of HO-1 may be mediated *via* the release of CO. Consistent with this notion is our previous demonstration that CO also suppressed the induction of apoptosis by ER stress in human ECs [28]. The anti-apoptotic effect of CO has been shown to be associated with a decrease in the expression of CHOP, of which principal function may be related to cell death induced by severe ER stress. CO blocked the CHOP expression in ECs treated with ER inducers [28]. Similarly, CHOP expression was down-regulated by CO in VSMCs [27]. The suppression of CHOP expression by CO corresponds with a study demonstrating that CHOP expression correlates negatively with the presence of Nrf2; CHOP expression in Nrf2-deficient cells is constitutively higher than that in wild-type cells, whereas Nrf2 over-expression attenuates CHOP accumulation during ER stress [29]. Given that Nrf2 can induce HO-1 expression, HO-1/CO system could be the effector molecule for down-regulating CHOP expression. As suggested, induced HO-1 may form dimer/oligomer and complex with accessory proteins [12,13] to generate CO. However the direct role of HO-1 dimer/oligomer by physically interacting with UPR pathways cannot be ruled out. Dominant-negative mutant at TMS of HO-1 may provide experimental evidence to dissect whether anchoring to ER membrane is essential for cytoprotective activity of HO-1. Because cell death following ER stress is implicated in the pathogenesis of metabolic diseases [30], the ability that HO-1-derived CO provides a protective advantage to cells during ER stress may be of clinical significance. Additionally, emerging evidence indicates that HO-1 inducers are endowed with potent anti-diabetic and insulin sensitizing effects besides their anti-inflammatory and antioxidant effects. Thus, approaches that target HO-1 or CO may offer a promising therapeutic modality in treating ER stress-mediated metabolic diseases.

6. Perspective

An imbalance between the actual protein-folding capacity of the ER and the demand placed on this organelle causes ER stress, and activates UPR, an adaptive response that counteracts ER stress. Activation of UPR, which intersects with many different inflammatory and stress signaling pathways, has been shown to be critical in chronic metabolic diseases, such as obesity, insulin resistance, and type 2 diabetes [31,32]. Indeed, both adipose tissue and the liver of mice chronically fed a high-fat diet exhibit characteristics of ER stress, including increased levels of phosphorylated PERK and IRE1α as well as increased JNK activity [33,34]. Moreover, mice deficient in XBP-1, a transcription factor that modulates the ER stress response, develop insulin resistance [30] and PERK-deficient mice also develop severe hyperglycemia because of defects in islet proliferation and increased apoptosis [33]. Additionally, patients with Wolcott–Rallison syndrome, a rare form of juvenile diabetes, are reported to have mutations in the *EIF2AK3* gene encoding PERK [34]. Thus, it is most likely that a high level of ER stress or defective ER stress signaling (*i.e.*, the UPR) could account for many pathophysiological events leading to metabolic diseases. Given that many of the adverse factors that are implicated in the pathophysiology of metabolic diseases can induce HO-1 expression, the HO-1 system may constitute a novel approach that could be explored against metabolic diseases. Therefore, the induced targeting of acute stress-protein, HO-1 against ER stress and its functional implications in the arena how organism develops defense machinery against a variety of metabolic stresses warrant further investigations.

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