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Forum Review

Molecular Basis of Heme Oxygenase-1 Induction: Implications for Chemoprevention and Chemoprotection

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ABSTRACT

Heme oxygenase (HO)-1, involved in the heme degradation process, is an important antioxidant enzyme. The induction of HO-1 gene expression, in response to diverse oxidative stimuli, represents a critical event in adaptive cellular response. Experimental models of various diseases, including acute inflammation, atherosclerosis, degenerative diseases, and carcinogenesis, have demonstrated that the induction of HO-1 can prevent or mitigate the symptoms associated with these ailments. Recent progress in our understanding of cellular signaling networks as critical modulators of gene transcription sheds light on the molecular basis of HO-1 gene expression. A panel of redox-sensitive transcription factors such as activator protein-1, nuclear factor-κB, and nuclear factor E2-related factor-2, and some of the upstream kinases have been identified as regulators of HO-1 gene induction. The scope of this review is limited to focus on molecular mechanisms underlying HO-1 expression and the significance of targeted induction of HO-1 as a strategy to achieve chemoprevention and chemoprotection. *Antioxid. Redox Signal.* 7, 1688–1703.

INTRODUCTION

Heme oxygenases (HOs) are microsomal enzymes that catalyze the oxidative cleavage of the porphyrin ring to generate biliverdin, free heme iron, and carbon monoxide (CO) (163). Multiple lines of evidence support the proposal that these catabolic end-products contribute to the part of physiological functions of HO such as antioxidative, anti-inflammatory, antiproliferative, and anti-apoptotic effects (39, 103). To date, three isoforms of mammalian HO with distinct patterns of tissue-specific gene expression have been identified: *HO-1*, *HO-2*, and *HO-3* (95, 96, 100). HO-1, the inducible isoform identical to 32-kDa heat shock protein (67), is evolutionarily conserved and ubiquitiously distributed in tissues (39). The expression of HO-1 is triggered by its substrate heme and diverse stress stimuli including ultraviolet radiation, hypoxia, inflammation, heavy metals, hydrogen peroxide, and nitric oxide (NO) (12, 62, 67, 106, 112, 168). Hence, the induction of HO-1 is one of the important events in cellular response to pro-oxidative and pro-inflammatory insults. Differential regulation of HO-1 has been observed among different species in relation to the variations in functional promoters and/or the expression of relevant transcriptional regulators. Activator protein (AP)-1, nuclear factor-κB (NF-κB), and nuclear factor E2-related factor-2 (Nrf2) are suggested to be key regulators mediating the up-regulation of HO-1 in response to external stimuli (4, 80, 103, 121, 160). Exposure to HO-1 inducers triggers activation of several upstream signaling kinases, such as the mitogen-activated protein kinases (MAPKs) (40), protein kinase A (PKA) (56, 134), protein kinase C (PKC) (115, 164), and phosphatidylinositol 3-kinase (PI3K) (85, 143), and subsequently increases DNA-binding activities of the aforementioned transcription factors.

In response to oxidative or electrophilic stress, cells attempt to initiate an adaptive response by activating a battery of defensive genes (34, 60). Severe oxidative stresses resulting in the accumulation of reactive oxygen species (ROS) and electrophiles cause damage to cell membrane and important

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cellular macromolecules, thus predisposing tissues to diverse pathological conditions including degenerative disorders, mutagenicity, premature aging, and cancer (17, 61, 177). HO-1 is induced as a protective mechanism to guard against oxidative damage of cellular lipids, proteins, and nucleoproteins (159). There has been increasing evidence supporting the notion that the targeted induction of HO-1 provides potent cytoprotective effects as assessed in various *in vitro* and *in vivo* models of cellular and tissue injury (13, 32, 154, 169). This article mainly focuses on the molecular basis as well as the significance of targeted induction of HO-1 as a potential chemopreventive/chemoprotective strategy.

MOLECULAR BASIS OF HO-1 INDUCTION

Like many other stress-responsive genes, the expression of HO-1 is dependent on the cell type, cellular microenvironment, intensity and duration of stimuli exposure, and species. In general, the induction of HO-1 involves the activation of intracellular signaling cascades consisting of upstream protein kinases and transcription factors (Table 1). The roles of key transcription factors and signaling kinases in the up-regulation of HO-1 are discussed in subsequent sections.

Roles of transcription factors in HO-1 induction

Analysis of the sequence and organization of the human, rat, mouse, and chicken HO-1 has revealed that the transcriptional control of this enzyme is governed by inducible regulatory elements localized in the 5′-flanking region of the HO-1 gene promoter (4, 79, 94, 151). These regulatory elements are binding sites for several redox-sensitive transcription factors, such as NF-κB, AP-1/2 (80), CCAAT/enhancer-binding protein (137), hypoxia-inducible factor-1 (HIF-1) (63, 84), adenosine 3′,5′-cyclic monophosphate (cAMP)-responsive element-binding protein (CREB) (74), and Nrf2 (5, 6). Notably, the human HO-1 gene contains a putative Maf recognition element (MARE) immediately downstream from the cadmium-responsive element (TGCTAGATTT) (160). Although the putative silencer sequence for the heat shock element has also been found in the human gene, this element is not functional and fails to confer the heat inducibility of HO-1 mRNA expression (151). Thus, variation in functional promoters among species has been observed, which may account for species differences in responding to stimuli causing HO-1 induction.

AP-1 and NF-κB. AP-1 and NF-κB are major transcription factors that can transactivate *HO-1* by binding to the promoter region of the gene. The transcription factor AP-1 is a dimeric combination of basic leucine zipper proteins of the Jun and Fos family, Jun dimerization partners, and the closely related activating transcription factor subfamilies (64). According to a study by Alam and Den (3), the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate-mediated HO-1 induction in mice required the AP-1 binding to the 5′-flanking region of the target gene. Subsequent studies have also demonstrated that the induction of HO-1 by other oxidative stimuli, such as heme (149), sodium arsenite, cobalt chloride (94), bacterial lipopolysaccharide (23), respirable particulate matters generated during incomplete combustion of fossil fuels (30), and cobalt protoporphyrin (149) is mediated via AP-1 activation. Since AP-1-mediated HO-1 induction can be attenuated by the antioxidant *N*-acetylcysteine (23), it is likely that ROS may play a critical role in the initiation of the signal transduction pathway leading to the AP-1-dependent HO-1 gene transcription.

Besides AP-1, other transcription factors such as AP-2 and NF-κB also play a crucial role in the induction of both activity and expression of HO-1 in response to the HO-1 substrate heme in the human erythroleukemic cell line K562 (80). External stimuli, such as hemin, cadmium (27), and lipopolysaccharide (178), can activate the HO-1 transcription through the NF-κB signaling pathway as the inhibition of NF-κB leads to attenuation of HO-1 induction by these agents (93). Moreover, Lavrovsky *et al.* (81) have demonstrated that overexpression of NF-κB in human hepatoblastoma-derived HepG2 cells results in an increase in HO-1 mRNA level. Curcumin-mediated HO-1 activation in human renal proximal tubule cells has also been found to be mediated via the activation of NF-κB (54).

Nrf2. Although the antioxidant response element (ARE) sequence located in the HO-1 gene promoter was initially considered to mediate stress responsiveness by interaction with the AP-1 transcription factor, the same sequence has recently been shown to interact with another transcription factor, Nrf2 (5, 6). Nrf2, a 66-kDa protein, is a member of the Cap'n'Collar family of basic leucine zipper transcription factors and plays an essential role in the ARE-mediated expression of phase II detoxifying, antioxidant, and stress-inducible genes including HO-1 (59). Collectively, a distinct set of Nrf2-regulated proteins function to detoxify xenobiotics, reduce oxidized proteins, maintain cellular reducing equivalents, disrupt redox cycling reactions, and counteract the noxious effects of ROS (61, 122).

Functional significance of Nrf2 in adaptive response to oxidative/nitrosative stress was observed in studies conducted with Nrf2-deficient mice, which were found to be more prone to toxic chemical-induced tissue injury (24, 25, 42). Nrf2-deficient mice also exhibited a significantly higher burden of benzo[*a*]pyrene-induced gastric neoplasia and were less responsive to the chemopreventive agent oltipraz [4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione] (132). According to Ishii *et al.* (58), Nrf2-deficient mouse peritoneal macrophages are more sensitive to toxic electrophiles.

Nrf2 is sequestered in the cytoplasm as an inactive complex with its cytosolic repressor kelch-like ECH-associated protein-1 (Keap1). Dissociation of Nrf2 from the inhibitory protein Keap1 is a prerequisite for nuclear translocation of Nrf2. After forming a heterodimer with small Maf protein, the active Nrf2 binds to *cis*-elements having common core sequences, alternatively known as MARE, ARE, or electrophile/stress response elements (83), thereby up-regulating a battery of target genes, including *HO-1* (Fig. 1).

In controlling the Nrf2/ARE-mediated gene expression in homeostasis, both Keap1 and Bach1 proteins are important. Keap1 functions as a repressor of Nrf2. It has been demonstrated that the Keap1-deficient mice showed high Nrf2

Table 1. Regulatory Mechanisms of HO-1 Induction by Diverse Stimuli

Transcriptional regulators	*Stimuli/conditions*	*Upstream signaling molecules*	*Animal model/ cell types (reference)*
NF-κB	Hemin and cadmium	ERK and p38 MAPK activation; independent of p53 status	Human gastric cancer (MKN-45 and MKN-28) cells (93)
	15d-PGJ_2	PI3K and p38 MAPK activation, but independent of peroxisome proliferator-activated receptor γ activation	Human lymphocytes (9)
	CO	p38 MAPK activation	Human endothelial cells (19)
	Lipopolysaccharide	p38 MAPK activation	Raw 264.7 monocytic cells (178)
AP-1	Phorone	JNK activation	Rat livers (117)
	Atrial natriuretic peptide	JNK and ERK activation	HUVEC (68)
	Sodium arsenite	ERK and p38 MAPK activation	Chicken hepatoma (LMH) cells (41)
	Hypoxia	ERK and p38 MAPK activation	Rat pulmonary aortic endothelial cells (140)
Nrf2	Cadmium chloride	p38 MAPK activation	MCF-7 cells (6)
	Carnosol	PI3K, ERK, p38, and JNK activation	PC12 cells (97)
	Spermine NONOate	ERK and p38 MAPK activation	Bovine vascular endothelial cells (20)
	Curcumin and CAPE	p38 MAPK activation	Porcine renal epithelial cells (15)
	15d-PGJ_2	Activation of PI3K and ERK	MCF-7 cells (70)
CREB	Oxidized phospholipids	PKA and PKC pathway p38 MAPK and ERK activation	HUVEC (74)
	SNP and 8-bromo-cGMP	Activation of PKG pathway	Primary cultures of rat hepatocytes (57)
E-Box	Sodium arsenite	Activation of p38 MAPK	Primary culture of rat hepatocytes (69)
CRE/AP-1	Sodium arsenite	JNK and c-Jun activation	Primary culture of rat hepatocytes (69)
Not available	Adrenocorticotropic hormone	PKA pathway	Mouse adrenocortical (Y1) cells (129)
	PKA-stimulating agent Bt_2cAMP	PKA pathway	Primary rat hepatocyte cultures (56)
	TNF-α and IL-1α Ca^{2+} signaling	PKC pathway; phospholipase activation;	Human vascular endothelial cells (164)
	Nerve growth factor	Mitogen-activated protein kinase kinase activation	PC12 cells (90)
	Hemin or CoPP	Dependent on bilirubin-mediated redox modulation of ERK phosphorylation	Cultured human airway smooth muscle cells (157)
	TGF-1β	p38 MAPK activation	Human lung cancer (A549) cells (114)
	Proteasome inhibitor (MG132)	p38 MAPK activation	Raw 264.7 macrophages (181)
	Quercetin	p38 MAPK activation	Rat aortic smooth muscle cells (89)
	Ischemic preconditioning	Activation of ERK, JNK, and p38 MAPK	Mouse lungs and vascular cells (188)
	Sodium arsenite	Akt activation	Cultured rat astrocytes (43)

CoPP, cobalt protoporphyrin; CRE, cAMP-response element; PKG, protein kinase G; SNP, sodium nitroprusside; TGF-1β, transforming growth factor-1β; TNF-α, tumor necrosis factor-α.

activity and died postnatally, probably because of malnutrition resulting from hyperkeratosis of the esophagus and forestomach (174). The role of Keap1 in regulating Nrf2 has recently been reviewed (75, 83). Bach1, a mammalian heme-responsive transcriptional repressor (116), blocks DNA binding of active Nrf2 by forming a heterodimer with small Maf proteins. The expression of HO-1 and Bach1 is inversely regulated (71). Although HO-1 is repressed by Bach1/small Maf heterodimers, it is activated by Nrf2/small Maf heterodimers (156). Recently, Dhakshinamoorthy *et al.* (35) have reported that Bach1 and Nrf2 competed with each other in regulating ARE-mediated gene expression in HepG2 cells. Thus, it is more likely that regulation of ARE-mediated gene expression is determined by a unique balance between Bach1 and Nrf2 inside the nucleus.

Other transcription factors. Other transcription factors reported to regulate HO-1 gene induction include HIF-1 and CREB. An increase in HIF-1 DNA-binding activity by hypoxia resulted in the induction of HO-1 gene expression in rat aortic vascular smooth muscle cells (84). In addition, transfection of human lung cancer A549 cells with HIF-1α small interfering RNA markedly attenuated hypoxia-induced HO-1 gene expression (50). However, both HIF-1-dependent and -independent mechanisms of HO-1 gene activation have been

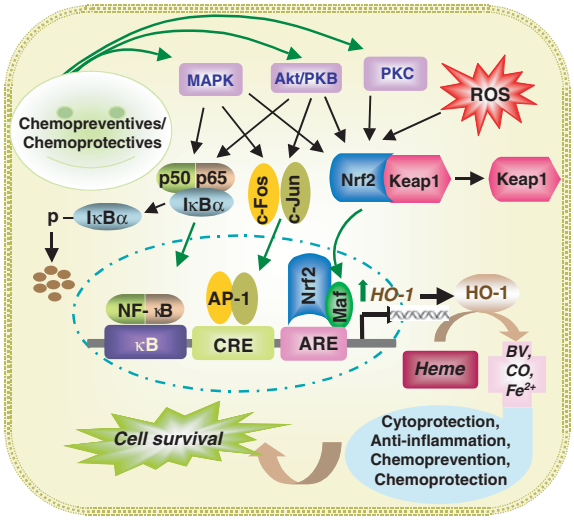

FIG. 1. A panel of redox-sensitive transcription factors such as AP-1, NF-κB, and Nrf2 and their upstream kinases have been identified as regulators of HO-1 gene induction. Under basal conditions, these signaling molecules are normally located in the cytoplasm. Upon challenge with inducing stimuli, the released active forms of these transcription factors translocate to the nucleus and are recruited to the specific DNA sequence leading to expression of the *HO-1* gene. BV, biliverdin; CRE, cAMP-response element; IκBα, inhibitor of NF-κB; PKB, protein kinase B.

noted (46). Recently, CREB has also been shown to be involved in the expression of HO-1 induced by oxidized phospholipids in human umbilical vein endothelial cells (HUVEC) (74).

Roles of upstream signaling molecules in mediating HO-1 induction

Various intracellular enzymes, mostly serine/threonine kinases, are major components of the cellular signaling network that respond to extracellular stimuli and target different transcription factors resulting in the modulation of gene expression (72, 155). Among the upstream signaling kinases, extracellular signal-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK have been considered to play major roles in controlling up-regulation of HO-1. Activation of one or more of these MAPKs by external stimuli triggers HO-1 gene expression. ERK, JNK, and p38 MAPK appear to be involved in regulating HO-1 gene transcription in response to ischemia-reperfusion (I/R) injury in mouse lung (188). ERK1/2 and p38 MAPK are involved in the induction of HO-1 gene transcription by sodium arsenite, oxidized phospholipids, NO, and hypoxia in hepatoma and endothelial cells (28, 41, 74, 138). However, the up-regulation of HO-1 via the MAPK pathway has a distinct cell type- and species-specific pattern.

Other signaling cascades that are likely to be involved in HO-1 induction include PKC, PKA, and PI3K. Several recent studies have addressed the role of PKC in the regulation of HO-1 gene expression (87, 115). According to the study by Numazawa *et al.* (115), treatment of human fibroblast WI-38 cells with a specific PKC inhibitor, Ro-31-8220, abrogated phorone- or 4-hydroxy-2,3-nonenal-induced HO-1 gene expression, suggesting that PKC regulates HO-1 induction. The same study also revealed that prolonged exposure of cells to 12-*O*-tetradecanoylphorbol 13-acetate failed to affect HO-1 expression, further suggesting that TPA-insensitive atypical PKC isoforms are involved in HO-1 induction. In addition, the activation of PKC has been shown to be involved in the induction of HO-1 by tumor necrosis factor-α, interleukin (IL)-1β, and oxidized phospholipids in human endothelial cells (74, 164). In contrast, transient glucose deprivation of cardiac fibroblasts resulted in the induction of HO-1 via the generation of ROS and activation of p38 MAPK, but not through translocation of PKC to cell membrane (161).

An increased intracellular level of either cAMP or 3′,5′-cyclic guanosine monophosphate (cGMP) can up-regulate HO-1 expression (56, 57, 127–129). Intracellular levels of cAMP are elevated by a large number of hormones and extracellular stimuli, resulting in the activation of PKA. Pretreatment with the PKA inhibitor KT5720 prevented the HO-1 mRNA expression induced by dibutyryl-cAMP (Bt_2cAMP) (56). Immenschuh *et al.* (56) reported that treatment of primary rat hepatocytes with PKA-stimulating agents, such as Bt_2cAMP and glucagon, resulted in a dose-dependent induction of HO-1. Like cAMP, an increase in cGMP via activation of soluble guanylate cyclase, either by NO-releasing agents or *via* the induction of inducible NO synthase, up-regulated HO-1 gene expression (104, 125–127).

The PI3K/Akt signaling pathway elicits the survival signal that has been correlated with inactivation of pro-apoptotic proteins and attenuation of the general stress-induced increase in ROS. The PI3K/Akt pathway controls the intracellular levels of ROS by regulating the expression of the antioxidant enzyme HO-1. Salinas *et al.* (143) have demonstrated that nerve growth factor protected against 6-hydroxydopamine-induced PC12 cell death *via* PI3K/Akt-dependent induction of the stress response protein HO-1. The same study also revealed that cells transfected with a membrane-targeted active version of Akt1 exhibited increased HO-1 expression, even in the absence of nerve growth factor, and attenuated the production of ROS and apoptosis in response to 6-hydroxydopamine. In addition, treatment of human vascular smooth muscle cells with simvastatin induced HO-1, which was abrogated by a specific inhibitor of PI3K, suggesting that induction of HO-1 is mediated *via* the PI3K/Akt pathway (85). A recent study from our laboratory also suggested involvement of the PI3K/Akt signaling pathway in the induction of HO-1 by 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) in human mammary cancer (MCF-7) cells (70). Other studies also addressed the role of the PI3K/Akt signaling pathway in 15d-PGJ_2-induced HO-1 expression (9, 91). The PI3K-mediated activation of Nrf2 has been proposed to be a major signaling pathway in HO-1 induction by hemin in human neuroblastoma SH-SY5Y cells (111). Besides its role in regulating HO-1 expression at the transcriptional level, Akt/protein kinase B has also been shown to induce post-translational modifications of HO-1 *via* phosphorylation of its serine-188 residue (144).

HO-1 AS A THERAPEUTIC TARGET

HO-1 guards against lipid peroxidation, protein oxidation, RNA/DNA damage, etc. HO-1-mediated cytoprotection is critical for those tissues that are vulnerable to oxidative stress (124, 148). The evolving paradigm of HO-1-mediated protection of cells and tissues is supported by several animal models of oxidant injury, *e.g.,* endotoxic shock (133), ischemia (176), hemorrhagic shock (162), hyperoxia (31, 129), and acute inflammation (179). Multiple lines of evidence suggest that the elevation of HO-1 confers resistance to stress-mediated cell injury, whereas blocking of HO activity abrogates cytoprotection, resulting in severe tissue damage (102, 139) (see Table 2 for more details).

Induction of HO-1 not only confers protection against oxidative stress, but also attenuates pro-inflammatory events (180). It has been reported that biliverdin, a product of the heme–HO-1 system, reduced formation of edema, leukocyte adhesion and migration, and production of pro-inflammatory cytokines, such as IL-6 and IL-1β (109). Moreover, regulatory interactions between either HO-1 and cyclooxygenase (COX) or HO-1 and NO have been reported (7, 131, 172). Modulation of signal transduction pathways by HO-1 or its catabolic products of heme degradation such as CO and bilirubin can control the activity or expression of COX and production of NO, thereby preventing the inflammatory response (88, 109, 141, 171). CO and bilirubin have been suggested to be responsible for anti-inflammatory and anti-apoptotic functions of HO-1 (18, 108, 120). CO possesses the capacity to inhibit platelet aggregation, regulates vascular tone, and inhibits smooth muscle proliferation (142). Biliverdin, which is converted into bilirubin (184), also exerts anti-inflammatory effects by decreasing mRNA expression of inducible NO synthase and COX-2 as well as the inflammatory cytokines IL-6 and IL-1β (109). Thus, HO-1 may confer protection against diverse diseases/conditions associated with oxidative stress and inflammatory tissue damage.

TABLE 2. HO-1 AS A THERAPEUTIC TARGET

Chemoprotective/chemopreventive responses	*Animal model/cell types and conditions of HO-1 induction*
Antioxidative and anti-inflammatory effects	
Prevent an increase of malondialdehyde and a decrease of glutathione in ethanol-treated hepatocytes	Human hepatocyte cells: pretreatment with cobalt protoporphyrin (92)
Inhibit rolling and adhesion of leukocytes in venules from hydrogen peroxide- and I/R-induced oxidative stress	Wistar rats: pretreatment with hemin (52)
Inhibit IL-8 production from endothelial cells in response to LPS-induced inflammation and xanthine oxidase-induced oxidant stress	HUVEC: pretreatment with hemin (21)
↓ Pro-inflammatory responses; ↓ endothelial dysfunction from oxidized low-density lipoprotein- or tumor necrosis factor-α-induced inflammatory stress	Mouse vascular endothelial cells: pretreatment with heme arginate (65)
Inhibit iNOS activity; ↓ cytokine release in mice subjected to zymosan-induced inflammation	Mouse air pouch: pretreatment with hemin (173)
↓ Mucosal injury, inflammation, and apoptotic cell death in rats with endotoxemia	Male Sprague-Dawley rats: pretreatment with glutamine (169)
↓ Both mRNA and protein levels of cytokines in the airway of mice from hypoxia-induced lung inflammation	Transgenic HO-1 overexpressing mice (185)
↓ Corneal inflammation, swelling, and new vessel invasion from extended contact lens wear-induced corneal inflammation	Rabbit ocular inflammation model: pretreatment with $SnCl_2$ (78)
Anti-apoptotic effects	
Prevent apoptotic liver injury by inhibition of caspase 3 activation from cytokine- and CD95-mediated apoptotic liver damage; ↑ survival of rats and ↓ cytokine expression from LPS-induced liver injury	Immune-mediated liver injury in mice model: pretreatment with cobalt protoporphyrin (145, 146)
↓ Apoptotic cell death and neutrophil-mediated oncosis	Galactosamine/endotoxin-induced shock in mice model: pretreatment with cobalt protoporphyrin (38)
Protect against tumor necrosis factor-induced apoptotic cell death	Mouse pancreatic beta cells: overexpression of HO-1 by transfection (166)
Protect cells against *Pseudomonas aeruginosa*-induced injury/apoptosis	Airway epithelial (IB3) cells from patients with cystic fibrosis: overexpression of HO-1 by transfection (189)
Protect cells against *Escherichia coli*-induced renal tubular epithelial cell death	Renal epithelial cells; pretreatment with sodium nitroprusside or hemin (29)
Protection against I/R injury	
↓ Infarct in cardiac area of rat from heart I/R injury	Female Sprague-Dawley rats: pretreatment with hemin (49)

(continued)

TABLE 2. CONTINUED

Chemoprotective/chemopreventive responses	*Animal model/cell types and conditions of HO-1 induction*
↓ Mucosal injury, inflammation, and improved intestinal transit I/R-induced injury	Male Sprague-Dawley rats: pretreatment with hemin (13)
↓ Portal venous resistance and ↑ bile production; improved liver function and diminished histological features of hepatocyte injury	Isolated perfusion rat liver: exposure to CO (10)
Restore microcirculatory parameters; ↓ hepatic inflammation, protects hepatocytes in mice subjected to hind limb I/R-induced injury	Mice exposed to CO (118)
Prevent hepatic microvascular perfusion deficits; ↓ hepatocyte death and ↓ serum bilirubin levels in mice with bilateral hind limb I/R-induced liver injury	Normotensive systemic inflammatory response syndrome mice: overexpression of HO-1 by transfection (99)
↓ Levels of plasma creatinine in mice with bilateral kidney I/R-induced acute renal failure	Mice: pretreatment with CO donors (170)
Prevention of graft rejection	
↑ Survival of recipient rat from prolonged intestinal I/R-induced injury	Rat small intestinal transplantation model: treatment with biliverdin (109)
↓ Lipid peroxidation, ↓ graft blood flow; ↓ pro-inflammatory mediator levels and ↓ extravasation of inflammatory infiltrates; ↑ survival of recipient rat from heart and kidney cold I/R-induced injury	Rat heart and kidney transplantation model: treatment with CO and biliverdin (110)
Inhibit releasing of inflammatory mediators and improved renal cortical blood flow in kidney grafts; preserve the glomerular vascular architecture and podocyte viability with less apoptosis of tubular epithelial cells and less macrophage infiltration; ↑ survival of recipient rat from kidney I/R-induced injury	Rat kidney transplantation model: exposure to CO (113)
↓ SGOT levels; ↓ number of apoptotic cells, ↓ iNOS expression, and ↑ anti-apoptotic Bcl-2 levels of recipient rat from hepatic cold I/R-induced injury	Rat liver transplantation model: pretreatment with hemin (175, 176)
Protection against neurodegenerative disorders	
↓ Changes in mitochondrial respiratory chain complex activity, protein nitrosation, and antioxidant status of astrocytes from LPS- and interferon-γ-induced nitrosative stress	Rat astrocytes: pretreatment with acetyl-L-carnitine (22)
Prevented cell loss and ↓ the number of dead cells from hydrogen peroxide-induced astrocyte apoptotic cell death	Rat astrocytes: pretreatment with sodium arsenite (43)
↑ Survival of glioma cells from cadmium chloride-induced cytotoxicity	C6 rat glioma cells: pretreatment with spermine NONOate (154)
↑ Cellular resistance to hydrogen peroxide-mediated cell death	Rat neuronal (Neuro 2A) cells: pretreatment with 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (32)
Prevent cells against serum deprivation-induced apoptosis	PC12 cells: pretreatment with nerve growth factor (90)
Miscellaneous	
Protect cells against cyclosporine A-induced nephrotoxicity	Rats: pretreatment with cobalt protoporphyrin (135)
Protect cells against more hydrogen peroxide-induced injury	Human proximal tubular (HK-2) cells: subjected to ischemic preconditioning or pretreatment with hemin (82)
Prevent reduction in postictal cerebral vascular reactivity in piglets from bicuculline-induced seizures	Piglets: pretreatment with cobalt protoporphyrin (123)
Inhibit endothelin-1-induced cardiac myocyte hypertrophy by inhibition of prohypertrophic calcineurin/NFAT pathway	Rat cardiac myocytes: either overexpression of HO-1 by transfection or pretreatment with biliverdin and CO donor (167)

CRE, cAMP-response element; iNOS, inducible NO synthase; LPS, lipopolysaccharide; NFAT, nuclear factor of activated T cells; SGOT, serum glutamic oxaloacetate transaminase.

HO-1-mediated protection of cells in atherosclerosis is one of the active areas of investigation. Zhang *et al.* (187) showed the significant resistance of the HO-1-transfected vascular smooth muscle cells to H_2O_2-induced cell death and lactate dehydrogenase leakage. Moreover, the growth-inhibitory potential of these transfected cells suggests that overexpression of HO-1 can potentially reduce the risk of atherosclerosis, partially because of its cellular protection against oxidative

injury and inhibitory effects on cellular proliferation. The implication of HO-1 induction in protecting blood vessels has been suggested by Yet *et al.* (183). According to this study, adenovirus-mediated gene transfer of HO-1 inhibited the development of atherosclerosis in apolipoprotein E-deficient mice. Moreover, ectopic expression of the HO-1 gene also provided a therapeutic effect on an acute lung injury in mice infected with influenza virus (37, 51).

The anti-apoptotic action of HO-1 has been shown to exert an inhibitory effect on cardiac hypertrophy. Ectopic expression of HO-1 significantly inhibited endothelin-1-induced hypertrophy in cardiac myocytes, while exogenous CO and biliverdin could mimic the growth-inhibitory effects of HO-1 (167). These results strongly suggest a critical role of HO-1 in preventing hypertrophy of the heart.

I/R injury is a multifactorial antigen-independent process that affects both early and late graft function after transplantation. The complex mechanism of I/R can be attributed to neutrophil accumulation and release of proinflammatory mediators and cytokines, which lead to cellular injury and graft rejection. HO-1 is one of the most critical cytoprotective proteins activated during these processes. Since HO-1 can amplify multiple intracellular cytoprotective signaling pathways, it may be considered as a novel therapeutic target for organ transplantation. Enhanced expression of HO-1 and production of HO-1 downstream mediators (bilirubin, ferritin, CO) are considered to confer protection against I/R injury. Application of the HO-1 inducer cobalt protoporphyrin or transfection with the HO-1 gene by use of an adenoviral vector prevented I/R injury in steatotic rat livers (10). The severity of hepatic I/R insult, as assessed by analysis of structural and functional parameters of liver injury, was also significantly attenuated by exogenous CO in an *ex vivo* rat model of ischemia followed by reperfusion (11). The p38 MAPK signaling pathway has been proposed to be the key regulatory mechanism by which CO prevents I/R insult. Moreover, inhibition of HO-1 increased I/R-induced tissue injuries, such as increased vascular resistance and hepatic sinusoidal congestion (11). The regimen of exogenous CO may have potential applications in preventing or mitigating I/R injury, and thus help expand the liver donor pool for transplantation. Preconditioning of tissue with a low concentration of oxidant induces HO-1 as an adaptive response, and after preconditioning, the exposure of the same tissue to a relatively high concentration of the oxidant fails to induce deleterious effects (159). Studies focusing on this aspect of HO-1 induction have been demonstrated in various I/R studies, such as *ex vivo* (11) and *in vivo* (175, 176) rat liver models. Moreover, stimulation or inhibition of HO-1 augmented or abolished oxidant preconditioning-mediated cytoprotection (76, 86), respectively.

Recently, the role of HO-1 in neuroprotection has received considerable attention, as it can operate a fundamental defensive mechanism for neurons exposed to oxidant challenge. HO-1 is potentially protective against oxidative brain injury by generating CO and bilirubin as a vasoactive molecule and a potent antioxidant, respectively. In Alzheimer's disease, β-amyloid-induced oxidative damage has been proposed as a major causative factor. Interaction between amyloid precursor protein and HO-1 protein leads to the inhibition of HO-1 activity, failure in neuroprotection, and subsequent neuronal cell death (158). Huang *et al.* (55) demonstrated that intraperitoneal injection of an HO-1 inhibitor, tin protoporphyrin, exhibited fewer surviving neurons than the control in a kainate-induced excitotoxic hippocampal injury in rats. Moreover, primary cultures of spinal motor neurons and glia from homozygous HO-1-null mice are more sensitive to NO-induced cytotoxicity than are HO-1-expressing cells, suggesting HO-1 as a frontline defense against NO-mediated neurotoxicity (16).

Oxidative stress is one of the etiologic factors for multistage carcinogenesis, which commences with initial transformation of cells, commonly known as initiation, *via* genetic and epigenetic changes such as mutagenicity, carcinogen-mediated DNA adduct formation, abnormal functioning of oncogenes and tumor suppressor genes, dysfunction of normal cellular signaling, etc. (155). Phase I xenobiotic metabolizing enzymes play a vital role in metabolic activation of carcinogen. Since HO-1 has been reported to inhibit Phase I enzymes (77, 107), the targeted induction of HO-1 may be implicated in chemoprevention, especially at the stage of tumor initiation. As an antioxidant enzyme, induction of HO-1 can also reduce the oxidant burden of cells, thereby blocking tumor initiation. Since inflammation is closely associated with tumor promotion (14, 33, 98), the anti-inflammatory effects of HO-1 or the products of the heme–HO-1 system (*e.g.,* CO and biliverdin) may signify the chemopreventive potential of HO-1 induction.

INDUCTION OF HO-1 BY CHEMOPREVENTIVE AGENTS

Chemoprevention, a promising strategy to prevent cancer, is defined as the use of either natural or synthetic substances or their combination to block, reverse, or retard the multistage process of carcinogenesis (155). Oxidative stress and inflammatory tissue damage have been closely associated with carcinogenesis. In view of the increasing evidence corroborating the antioxidant and anti-inflammatory effects of HO-1 products, the induction of this enzyme or its catalytic activity by either natural or synthetic compounds may represent an effective strategy to intervene in multistage carcinogenesis.

Chemopreventive phytochemicals

A wide variety of phytochemicals including curcumin, caffeic acid phenethyl ester (CAPE), sulforaphane, carnosol, and resveratrol have been recognized as potential chemopreventive agents. Cytoprotective, anti-inflammatory, and antioxidant effects exerted by these phytochemicals *via* HO-1 induction may contribute to their chemopreventive activity.

Curcumin. Curcumin, a major active component of the food flavor turmeric extracted from the dried rhizomes of *Curcuma longa* Linn. (Zingiberaceae), has been used for the treatment of a variety of inflammatory conditions and other disorders. In fact, curcumin has been reported to possess effective anti-inflammatory, antioxidant, and anticarcinogenic activities.

Curcumin, because of the presence of electrophilic centres in its structure, can act as a Michael reaction acceptor and is able to induce the activities of phase II detoxification enzymes (36). Recently, up-regulation of HO-1 expression by low concentrations of curcumin has been reported to contribute to its cytoprotective effect and greatly potentiated the ability of the endothelial cells to resist oxidant-mediated cell injury under hypoxic conditions (105). This enhancement occurred at a transcriptional level since hypoxia stimulated HO-1 mRNA expression more rapidly and strongly in the presence of curcumin. It is conceivable that curcumin could be used as a pharmacological "preconditioning" agent to activate the intracellular defense pathways in organs or tissues in response to oxidant-mediated injury. While curcumin can inhibit growth of cancer cells (1,73), it can up-regulate HO-1 expression and activity in normal cells (105, 147), thereby protecting against oxidative stress-mediated DNA damage and subsequent initiation of carcinogenesis process. Curcumin induced HO-1 gene expression in porcine renal epithelial (LLC-PK_1) and rat kidney epithelial (NRK) cells by dissociating the Nrf2-Keap1 complex and facilitating Nrf2 binding to ARE, which were suggested to be mediated *via* activation of p38 MAPK (15). In addition, the treatment of human renal proximal tubule cells with curcumin induced expression of HO-1 mRNA and protein, in part *via* activation of the NF-κB signaling pathway (54).

CAPE. CAPE, a polyphenolic compound from honey bee propolis, has been reported to induce HO-1 in vascular endothelial, neuronal, and renal epithelial cells (15, 147). Balogun *et al.* (15) reported that CAPE stimulated HO-1 gene expression by inducing dissociation of the Nrf2–Keap1 complex, leading to increased Nrf2 binding to the resident HO-1 ARE. Similar to curcumin, CAPE also contains electrophilic α,β-unsaturated carbonyl moieties, which can form Michael adducts selectively with nucleophiles, such as cysteine thiols present in Keap1, thereby facilitating nuclear translocation of Nrf2 (36).

Sulforaphane. The isothiocyanate sulforaphane, a constituent of cruciferous vegetables, has been intensively investigated for its bifunctional chemopreventive effects mediated through the inhibition of phase I enzymes and induction of phase II enzymes (77, 107). Sulforaphane can also induce apoptosis and modulate cell-cycle progression of highly proliferating cancer cells (152, 153). The compound also increases the binding of Nrf2 to ARE, resulting in the induction of a battery of phase II detoxification genes, including HO-1 (186). We recently found that treatment of rat pheochromocytoma PC12 cells with sulforaphane induced HO-1 protein and mRNA expression, which appeared to be mediated through activation of Nrf2 (A.P. and Y.-J.S., unpublished data).

Naturally occurring organosulfur compounds. Organosulfur compounds (*e.g.,* allyl sulfide, diallyl disulfide, diallyl trisulfide) present in garlic have been shown to possess chemoprotective and chemopreventive activities (53). Allyl sulfides reduce the risk of cancer by blocking carcinogen activation and/or enhancing detoxification of activated carcinogens. Several studies have demonstrated that organosulfur compounds can suppress metabolic activation of carcinogen, thereby preventing chemical toxicity and carcinogenesis (101, 182). In addition, the induction of antioxidant and phase II detoxification enzymes by organosulfur compounds has recently been reported (48, 150). Since allylsulfides undergo metabolic conversion to form sulfone derivatives (45), which may act as electrophiles, organosulfur compounds are thought to target the Nrf2–Keap1 complex, thereby activating Nrf2-regulated gene transcription and ARE activity. Supporting this hypothesis, Chen *et al.* (26) recently reported that treatment of human hepatoma HepG2 cells with various organosulfur compounds resulted in Nrf2 activation leading to the induction of HO-1. Similarly, Nrf2-mediated HO-1 induction by diallyl sulfide in HepG2 cells has been reported by Gong *et al*. (47). While diallyl trisulfide-induced ARE activity has been shown to be mediated *via* Ca^{2+}-dependent signaling, but not that of MAPKs or PKC (26), diallyl sulfide caused ROS-dependent activation of ERK and p38 MAPK in the same cell line (47), thereby facilitating nuclear translocation of Nrf2 and subsequent induction of the HO-1 gene. The differential effects of organosulfur compounds on the MAPK-mediated activation of Nrf2 and HO-1 induction may be due to structural difference in the number of sulfur moieties and the length of the alkyl side chain, which may confer varying degrees of electrophilicity to parent compounds as well as their active metabolites.

Miscellaneous phytochemicals. Resveratrol, at a low concentration, induced HO-1 in human aortic smooth muscle cells in a time- and concentration-dependent manner, which was mediated *via* activation of the NF-κB signaling pathway. Although resveratrol inhibited NF-κB signaling in different cell types at relatively high concentrations (≥20 μ*M*), previous studies suggested that the compound at a relatively low concentration exhibited a pro-oxidant effect (2). We recently found that treatment of PC12 cells with resveratrol resulted in the induction of HO-1, which was mediated *via* ERK- and PI3K-dependent activation of Nrf2 (C. Chen and Y.-J.S., unpublished data). The induction of HO-1 protein and its mRNA transcript by carnosol, an antioxidant present in rosemary, was mediated *via* the PI3K/Akt signaling pathway (97). Recently, Foresti *et al.* (44) demonstrated that rosolic acid, a constituent derived from rhizomes of *Plantago asiatica* L., induced both expression and activity of HO-1 in bovine aortic endothelial cells. According to this study, an increase in intra- and extracellular thiols markedly reduced rosolic acid-induced HO-1 expression, while MAPK played only a minor role.

Synthetic antioxidants

Some of the synthetic phase II enzyme inducers (oltipraz and related dithiolethiones) and COX-2 inhibitors that have been shown to reduce the risk of developing certain types of cancer also modulate the HO-1 expression and/or activity. Selective COX-2 inhibitors have been suggested to modulate NO-inducible expression of HO-1. Co-incubation of RAW264.7 cells with a selective COX-2 inhibitor, SC58125, and the NO-donor spermine nonoate exhibited the synergistic effect on HO-1 induction mainly at the transcriptional level (8). The induction of HO-1 by NO and its potentiation by the

COX-2 inhibitor may play a role in attenuating inflammatory responses. Vicente *et al.* (173) reported that administration of zymosan induced HO-1 protein expression in a mouse air pouch model and also observed an increased expression of HO-1 with concomitant inhibition of COX-2 expression and prostaglandin E_2 levels in peritoneal macrophages from hemin-injected mice. In addition, IL-1β strongly induced HO-1 mRNA in the presence of indomethacin (165). Although the direct association between anti-tumorigenic activity and HO-1 induction has not been demonstrated, the enhancement of HO-1 expression by COX inhibitors with chemopreventive activity suggests the potential of HO-1 inducers in achieving chemoprevention.

Oltipraz and related dithiolethiones exert their chemopreventive activities by enhancing the expression of carcinogen detoxification and antioxidant genes including HO-1 (66, 136). Oltipraz has been shown to protect against acute toxicities mediated by carbon tetrachloride, acetaminophen, allylalcohol, and aflatoxin in laboratory animals (75). According to Primiano *et al.* (130), treatment of rats with 1,2-dithiole-3-thione resulted in a significant increase in hepatic HO-1 activity that corresponded to increased HO-1 protein levels. The chemopreventive effects of oltipraz and related thiols have been attributed to their ability to reduce the formation of reactive metabolites of chemicals and/or to enhance their detoxification (75).

CONCLUSION

Compelling evidence presented in this review and the literature precedents provides strong support for the role of HO-1 as one of the prime components of cellular defense mechanisms. Further, the up-regulation of HO-1, mediated through transcriptional regulation by AP-1, NF-κB, and Nrf2, points to the central role of those transcription factors in the maintenance of the cellular redox homeostasis. It appears that enhanced oxidative or nitrosative stress during inflammation is accompanied by compensatory induction of HO-1. In addition, HO-1, as an antioxidant enzyme, can also prevent oxidative damage of DNA, thereby preventing initiation of the carcinogenesis or suppressing the promotion that is linked to oxidative or pro-inflammatory tissue damage. Induction of HO-1 is hence recognized as one of the most fascinating targets for chemoprevention and chemoprotection research.

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ABBREVIATIONS

AP, activator protein; ARE, antioxidant response element; Bt_2cAMP, dibutyryl 3′,5′-cyclic adenosine monophosphate; cAMP, 3′,5′-cyclic adenosine monophosphate; CAPE, caffeic acid phenethyl ester; C/EBP, CCAAT enhancer binding protein; cGMP, 3′,5′-cyclic guanosine monophosphate; CO, carbon monoxide; COX, cyclooxygenase; 15d-PGJ_2, 15-deoxy-$\delta^{12,14}$-prostaglandin J_2; ERK, extracellular signal-regulated kinase; HIF-1, hypoxia-inducible factor-1; HO, heme oxygenase; HUVEC, human umbilical vein endothelial cells; IL, interleukin; I/R, ischemia/reperfusion; JNK, c-Jun N-terminal kinase; Keap1, kelch-like ECH-associated protein-1; MAPK, mitogen-activated protein kinase; MARE, Maf recognition element; NF-κB, nuclear factor-κB; NO, nitric oxide; Nrf2, nuclear factor E2-related factor-2; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC, protein kinase C; ROS, reactive oxygen species.

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