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REVIEW

A review on heme oxygenase-1 induction: is it a necessary evil

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Abstract
Heme oxygenase-1 (HO-1) is considered to be the main protein in diseases arising as a result of oxidative and inflammatory insults. Tremendous research has been carried out on HO-1 since years, pertaining its cytoprotective effect against oxidative injury and other cellular stresses. HO-1, by regulating intracellular levels of pro-oxidant heme, or by other benefits of its by-products such as carbon monoxide (CO) and biliverdin (BV) had become an important candidate protein to be up-regulated to combat diverse stressful events. Although the beneficial effects of HO-1 induction have been reported in a number of cells and tissues, a growing body of evidence indicates that this increased HO-1 expression may lead to the progression of several diseases such as neurodegeneration, carcinogenesis. But it is not clear, what accounts for the increased expression of HO-1 in cells and tissues. The observed friendly role of HO-1 in a wide range of stress conditions since times is now doubtful. Therefore, more studies are needed to elucidate the exact role of HO-1 in various stressful events. Being more concise, elucidating the effect of HO-1 up-regulation on critical genes involved in particular diseases such as cancer will help to a larger extent to comprehend the exact role of HO-1. This review will assist in understanding the dual role (protective and detrimental) of HO-1 and the signaling pathway involved and will help in unraveling the doubtful role of HO-1 induction.

Keywords Bilirubin · Carbon monoxide · Cytoprotection · Heme · Heme oxygenase · Oxidative dysregulation

Introduction

Heme oxygenase (HO) plays a vital role in the catabolism of heme and yields equimolar amounts of BV, CO and free iron [1]. Heme oxygenase is responsible for cleaving at the alpha-methene bridge of the heme ring to form biliverdin, which is acted upon by the biliverdin reductase to form bilirubin (BR). But if after cleavage, the heme remains still attached to the globin molecule, then verdoglobin is formed.

To date, two isoforms of HO (HO-1 and HO-2) have been reported in mammals and a third one, i.e., HO-3 has been proposed by Hayashi and his colleagues, while as four HO isoforms (HO-1, HO-2, HO-3, and HO-4) have been identified in plants. Among different HO isoforms, HO-1 is considered to be of keen research interest as its expression level is induced during various pathophysiological conditions [2].

Human HO-1 has a molecular weight of 32.8 kDa (kilodalton), composed of 288 amino acids and shares about 80% amino acid homology with rat HO-1. HO-1 has emerged as an ideal cytoprotective agent and modulation in its expression and activity levels could provide a potential therapeutic value [3]. HO-1 is associated with smooth endoplasm reticulum (SER), but is also localized in mitochondria nuclei and caveoli [4]. It has been found that mitochondrial HO-1 fraction is increased in lung epithelial cells when exposed with hemin, lipopolysaccharide (LPS) and cigarette smoke [5]. The increased translocation of HO-1 to mitochondria protects epithelial cells against mitochondria associated cell death [6]. Another study in rats, also reported enhanced translocation of HO-1 to the mitochondria of the gastric mucosa after indomethacin treatment [7]. This enhanced translocation of HO-1 to mitochondria has been associated with the decline in lipid peroxidation and also ameliorates gastric mucosal injury [7]. Under stress conditions, HO-1 gets translocated to nucleus where it regulates its own

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expression [8]. Nuclear localization of HO-1 has been found in different cancerous tissues such as oral, lung and prostate, and has been linked with the tumor progression [2]. Translocation of HO-1 to nucleus is mediated by its proteolytic cleavage, which releases HO-1 from SER and subsequently allows its entry to nucleus [4]. Nuclear HO-1 has been linked to tumor growth and protection against oxidative stress by up-regulating antioxidant genes [9] (Table 1).

Induction of HO-1

HO-1 is induced in response to panoply of stimuli such as hypoxia, oxidative stress, cytokines, LPS, heavy metals, in biological systems. Since HO-1 induction is a widely accepted strategy used by cells to neutralize a variety of stress conditions [10], the targeted induction of this powerful enzyme may be a beneficial therapeutic strategy against different diseases arising as a result of inappropriate immune response and oxidative dysregulation. Particularly, the identification of non-cytotoxic HO-1 inducers may represent a novel approach to combat various oxidative and inflammatory responses [11]. Many natural compounds have been confirmed to be effective non-cytotoxic HO-1 inducers in hepatic cellular models [12]. A majority of HO-1 inducers are present in plants that are being widely used as flavoring agents, food, spices and traditional medicinal plants. Besides toxicity, a possible concern with the use of pharmacological inducers of HO-1 relates to the GT dinucleotide repeat length in the HO-1 promoter [13].

Lipopolysaccharide is an important molecule present in the outer membrane of Gram-negative bacteria. LPS is known to activate toll-like receptor 4 (TLR4) which leads to a signaling cascade, thereby activating transcription factor nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPKs) and interferon response factors (IRFs) [14]. The cascade in turn causes release of pro-inflammatory mediators including interleukin-1 (IL-1), IL-6, IL-12, tumor necrosis factor-α (TNF), interferon (IFN)-γ, β and nitric oxide [15]. LPS-induced HO-1 induction is cytoprotective against pulmonary inflammation and decreases migration of polymorphonuclear leukocytes (PMNs) to lungs in response [16]. LPS can activate all the three mitogen-activated protein kinase (MAPK) pathways. However, it is not necessary that these pathways activated may be involved in HO-1 induction by LPS. Moreover, HO-1 induction by these MAPK pathways shows inducer-dependent specificity. Exogenous treatment of PGE_2 has been found to suppress the HO-1 expression and enhances the LPS-induced cyclooxygenase-2 (COX-2) expression in RAW 264.7 macrophages [17]. Moreover, LPS has been found to induce the expression of HO-1 in monocytes and thereby provides protection against the excessive inflammatory responses [18]. It has been found

Table 1 Different isoforms of HO in *Homo sapiens, Arabidopsis thaliana, Drosophila melanogaster, Arabidopsis thaliana, Danio rerio, Mus musculus* and *Sus scrofa*

Organism name	Name/gene ID	Description	Location
Homo sapiens	HMOX1 ID: 3162	Heme oxygenase-1	Chromosome 22, NC_000022.11 (35381067..35394214)
	HMOX2 ID: 3163	Heme oxygenase-2	Chromosome 16, NC_000016.10 (4474697..4510347)
Drosophila melanogaster	HO ID: 41407	Heme oxygenase	Chromosome 3R, NT_033777.3 (11679743..11680976)
Arabidopsis thaliana	TED4 ID: 817208	Plant heme oxygenase(decyclizing) family protein	Chromosome 2, NC_003071.7 (11341548..11343693)
	HO2 ID: 817196	Heme oxygenase-2	Chromosome 2, NC_003071.7 (11291148..11293575, complement)
	HO3 ID: 843308	Heme oxygenase-3	Chromosome 1, NC_003070.9 (26226731..26228580)
	HO4 ID: 842199	Heme oxygenase-4	Chromosome 1, NC_003070.9 (21627758..21630118, complement)
Danio rerio	HMOX1A ID: 791518	Heme oxygenase-1a	Chromosome 3, NC_007114.7 (26011482..26017592, complement)
	HMOX2A ID: 100002875	Heme oxygenase-2a	Chromosome 22, NC_007133.7 (26857686..26865206, complement)
	HMOX2B ID: 100329531	Heme oxygenase-2b	Chromosome 3, NC_007114.7 (11957118..11972630, complement)
Mus musculus	HMOX1 ID: 15368	Heme oxygenase-1	Chromosome 8, NC_000074.6 (75093618..75100593)
	HMOX2 ID: 15369	Heme oxygenase-2	Chromosome 16, NC_000082.6 (4726361..4766741)
Sus scrofa	HMOX2 ID: 396622	Heme oxygenase-2	Chromosome 3, NC_010445.4 (37829044..37868163, complement)

The data have been collected from NCBI

that two enhancer regions in HO-1 gene mediate its activation in response to LPS in mouse [19].

Several chemicals and drugs from plant origin have been reported to induce HO-1 expression [20]. Among them is curcumin (a polyphenolic compound isolated from the rhizome of *Curcuma longa*), which exerts a significant anti-inflammatory activity [21] and a well-characterized non-cytotoxic HO-1 inducer in endothelial cells, astrocytes, macrophages and muscle cells [22]. Carnosol is a naturally occurring bioactive phenolic compound that has been associated with the stimulation of HO-1 expression in a time-dependent manner [23]. Thus, active constituents from different medicinal plants may prove to be potent inducers of HO-1 enzyme, and provide many therapeutic agents for the amelioration of inflammation and oxidative stress. Fraxetin (a coumarin derivative) induces HO-1 expression via activation of AMPKα/Nrf2 or Akt/Nrf2 pathway [24].

Signaling cascades leading to HO-1 activation

Earlier studies indicate that different HO-1 inducers activate diverse protein phosphorylation-dependent signaling pathways that ultimately regulate the HMOX1 gene expression by activating a wide variety of transcription factors. Different intracellular signaling molecules and transcription factors are associated with HO-1 expressions such as Nrf2, MAPK, Bric a brac, Tramtrack and Broad complex (BTB) and cap 'n' collar (CNC) homologue 1 (Bach1), AP-1 and NF-κB [25]. Mitogen-activated protein kinase (MAPK) is one of the most essential signaling molecule associated with HO-1 induction by non-toxic phytochemicals and drugs [26]. Other signaling molecules such as phosphatidylinositol 3-kinase (PI3K), tyrosine kinases and protein kinases A, B, C, and G are known to play role in HO-1 induction [27]. But unfortunately, a little work has been done on the role of these kinases in HO-1 induction. HO-1 expression is primarily regulated at the transcription level and different cis-acting regulatory elements (REs) are associated to mediate the basal and inducible expression levels of HO-1 gene. Two upstream enhancer regions (E1 and E2) play major functional roles for redox-dependent induction of HO-1. Both E1 and E2 enhancer regions contain several antioxidant response elements (AREs). For further details see refer to Fig. 1.

Consequences of heme degradation by HO-1

Several studies have reported the protective effects conferred by HO-1 through its ability to degrade heme. However, the actual mechanism of its action has not been yet completely revealed. The most accepted mechanism suggests that the by-products of the heme degradation [mostly carbon monoxide (CO) and bilirubin (BR)] mediate its cytoprotective effects [10]. However, these metabolic by-products have been seen to either ameliorate or exacerbate

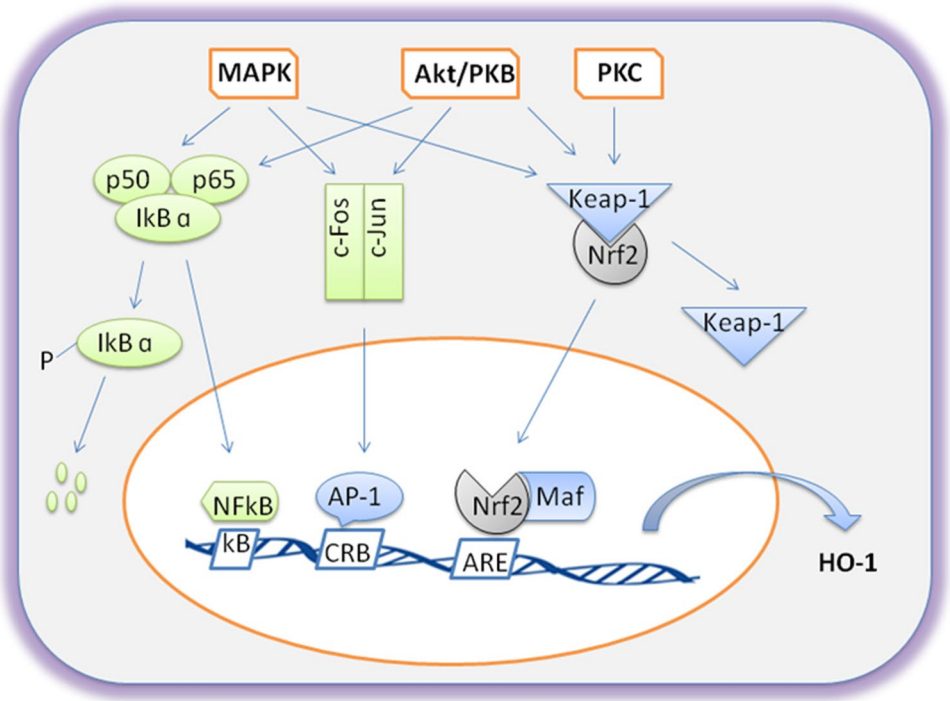

Fig. 1 Showing different HO-1 induction pathways: transcription factors suc as AP-1, Nrf2 and NF-κB remain localized in cytosol under normal conditions. Under external stimuli, these transcriptional factors get activated and tranlocate to the nucleus. Within the nucleus they bind specifically to the DNA sequence and leads to the HO-1 transcription

stress-related diseases depending upon particular disease models employed, the intensity of HO-1 expression and the existing redox microenvironment (as shown in Fig. 2).

Protective effects of HO-1 induction implicated in several diseases

The mechanism of heme degradation employed by HO-1 has proven to be an effective method of suppressing oxidative dysregulation, inappropriate immune response and related disorders. So the targeted induction of HO-1, particularly by non-toxic inducers, has been established as a potent therapeutic means of curing stress-related diseases.

HO-1 as an anti-inflammatory agent

HO-1 has been regarded as a potent anti-inflammatory enzyme, as evidenced by a large number of studies. The significance of HO-1 is illustrated by HO-1 knockdown studies (using HO-$1^{-/-}$mice), which develop the progressive inflammatory disease and show a robust increase in the levels of pro-inflammatory cytokines (IL-1β, interferon-γ, TNF, and interleukin-6) [6, 28].

The actual underlying mechanism responsible for the anti-inflammatory properties of HO-1 is not fully known. However, the signaling action of CO together with the antioxidant properties shown by biliverdin/bilirubin and iron sequestration by ferritin could all contribute in the amelioration of inflammation (as described above). CO has been seen to act as an efficient anti-inflammatory agent in several in vitro and in vivo models of inflammation. CO has been reported to significantly impair the nitric oxide (NO) generation and TNF or IL-6 production in lipopolysaccharide-stimulated macrophages [29]. Further, Morse and his coworkers observed that these effects of CO might be caused by interfering of CO with AP-1 activity via a c-Jun N-terminal kinase (JNK)-dependent pathway [30]. CO also increases production of anti-inflammatory cytokine, IL-10, in macrophages [31]. BV/BR production and Fe^{2+} chelation reduce adhesion of leukocytes to vascular endothelium by causing certain changes in expression of various adhesion molecules such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and thus reduce inflammation [32]. The HO-1 promoter contains binding sites for various transcription factors such as NF-kB, AP-1, and AP-2 as well as motifs for glucocorticoid-responsive elements. HO-1 has been seen to be capable of modulating activities of these transcription factors leading to different protective properties. For instance, it has been observed that upon up-regulating the HO enzyme with hemin, NF-kB expression was down-regulated in different in vivo models of type 2 diabetes [33], as well as different hypertensive models. Likewise, HO-1 has been found to be dispensable for the anti-inflammatory activity of intravenous immunoglobulin G (IVIG) [34].

Neuroprotective role of HO-1

The functioning of the brain is largely dependent on the constitutive supply of oxygen, as brain consumes an ample percentage (up to 50%) of total oxygen supplied to the body. However, under normal physiological condition, 2–5% of total oxygen consumed by cells is transformed into reactive oxygen species (ROS). However, if there is excessive and

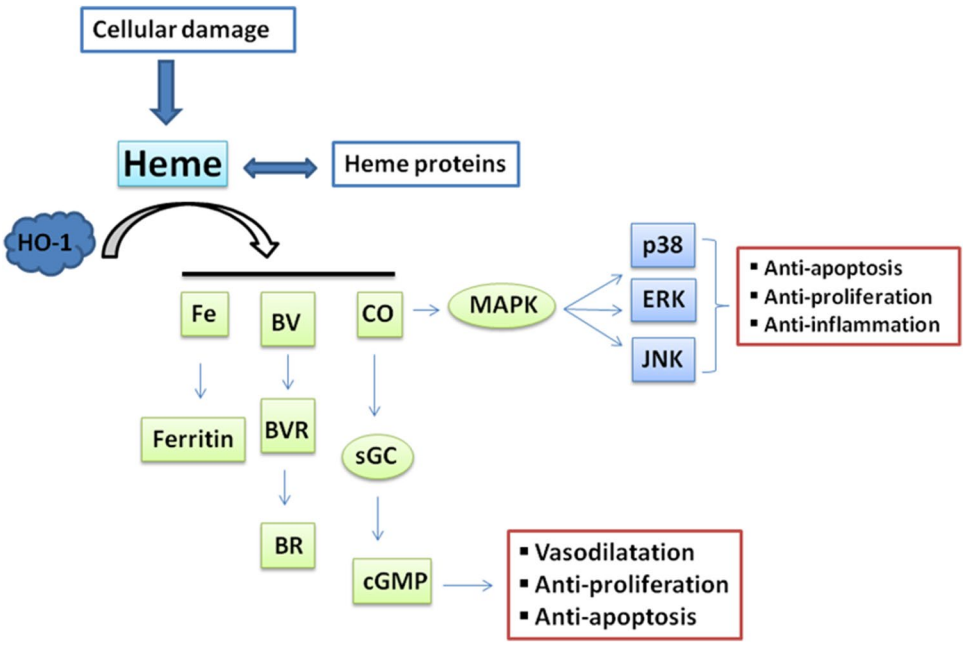

Fig. 2 Showing the cytoprotective mechanism of HO-1 by-products: HO-1 is responsible for the degradation of heme derived from heme proteins and during cell injury. HO-1 by-products such as CO and biliverdin had become important candidate proteins to be up-regulated to combat diverse stressful events

unregulated ROS production in the central nervous system (CNS), it leads to several neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [35]. However, there is emerging evidence that HO-1 expression helps in preventing the pathogenesis of various neurodegenerative diseases. HO-1 induction has been seen to implicate a neuroprotective role on exposure to a variety of noxious stimuli, both in animal models as well as in tissue culture. HO-1 induction occurs in both neuronal and non-neuronal brain cells. Astrocytes show more robust HO-1 response than neurons [36]. Many studies illustrate the protective role of HO-1 against various neurodegenerative disorders. Cerebellar granule cells of transgenic mice designed to overexpress HO-1 in neurons were relatively resistant for oxidative stress-mediated cell death [37]. When HO-1 was overexpressed in neuronal cells, they were seen to be resistant to oxidative damage induced by glutamate and H_2O_2. Similarly, transfection of neuroblastoma cell lines with HO-1 cDNA was seen to decrease the susceptibility of the cells to oxidative damage caused by H_2O_2 [38]. Also, HO-1, when overexpressed, protects neurons from toxicity induced by 1-methyl-4-phenylpyridinium (MPP) by increasing the expression of glial cell-derived neurotrophic factor [39]. The flavonoid quercetin induces HO-1 expression and inhibits iNOS expression in BV-2 cells [40], however, when these cells were treated with HO-1 antisense oligodeoxynucleotide, inducible nitric oxide synthase (iNOS) expression was no more seen to be inhibited. HO-1 induction affects other parameters of inflammation as well. For instance, in rat cortical astrocytes, HO-1 activity seems to be linked to the level of prostaglandin E2 production [41]. Conversely, down-regulation or knocking out HO-1 increases the susceptibility to oxidative and other stress challenges. It has been reported that astrocytes taken from HO-1 knockout mice show more vulnerability to toxicity induced by hemin relative to wild-type cells [42]. Moreover, the protective role of HO-1 has been attributed not only to its antioxidant properties but also to its potential of degradation of tau and α-synuclein by proteasomes [43]. Furthermore, HO-1 localized in mitochondria has been reported to reduce oxidative damage in renal epithelial cells [44].

Protective role of HO-1 in cardiovascular diseases

The incidence of cardiovascular diseases is so high that only in the United States it accounted for 33.6% of all deaths in 2007 [45]. A primary function of HO-1 in maintaining cardiac homeostasis was first shown by Ewing and his coworkers by observing an increased HO-1 expression in the heart in response to hyperthermia [46]. Further, in HO-1 knockout (HO-$1^{-/-}$) mice studies, hypoxia induces severe right ventricular dilatation and infarction in comparison to wild-type mice [47]. Besides, many studies using cardiac-specific HO-1 transgenic mice models revealed reduced myocardial infarct size following ischemia/reperfusion injury due to HO-1 overexpression [48]. Moreover, in the heart failure model, overexpressed HO-1 promotes neovascularization and ameliorates apoptosis [49]. To avoid superfluous side effects of constitutive overexpression of HO-1, hypoxia-regulated HO-1 gene vector was designed which could turn on only in myocardial ischemic condition [50]. Previous studies have found that QT interval prolongation is a risk factor for cardiovascular risk [51]. Intriguingly, particulate air pollution and iron metabolism genes (including heme oxygenase-1) have been involved in QT prolongation [52]. Also, HO-1 is required for angiogenic function of bone marrow-derived progenitor cells [53] and provides protection from cardiovascular diseases [54]. It has been further found that HO-1 plays an important role in endothelial repair and vascular protection [55] and thus providing intriguing aspects of endothelial progenitor cells (EPC)—therapeutic potential [56].

HO-1 in renal function

The kidney encounters different toxins, which includes both exogenous and endogenous ones. Free heme is the main molecule which is responsible for inducing oxidative stress and ultimately results in HO-1 induction [57]. It has been observed that HO-1 induction occurs in different substructures of kidney such as renal interstitium, proximal tubules, renal mononuclear phagocytes (RMPs) and glomeruli in response to injury [58]. HO-1 induction has been linked with the restoration of renal function in animals subjected to ischemia/reperfusion injury (IRI) [59]. It has been observed that expression level of HO-1 increased many folds in rats treated with angiotensin II (induces renal injury) and thus provides protection against hypertension [60]. Gentamicin (GM)-mediated renal dysfunction can be effectively improved by inducing HO-1 expression [61].

Hepatoprotective role of HO-1

HO-1 induction has been observed to play a hepatoprotective against different injuries [62]. A wide variety of hepatotoxic conditions (ischemia reperfusion, hemorrhagic shock, hypoxia and endotoxin) and chemicals (halothane isoflurane, heavy metals, acetaminophen and reactive oxygen species) have been observed to induce HO-1 expression, and thereby protects liver against damage [25]. Curcumin has been found to induce HO-1, and thereby protects hepatocytes against oxidative injury [63]. Similarly, treatment with Majoon-e-Dabeed-ul-Ward (a unani formulation) has been observed to protect lung cells against ethanol-induced cell death by inducing HO-1 [64]. Up-regulation of HO-1 expression

either chemically or by adenoviral gene transfer method has been observed to rescue the mice against the apoptotic liver damage [65, 66]. Recently, polyphenol-enriched fraction from *folium microcos* has been found to show hepatoprotective effect against the liver damage associated with the acetaminophen treatment [67].

HO-1 and diabetes

It has been observed that up-regulation of HO-1 is capable of increasing insulin secretion, and thereby reduce extra blood glucose (hyperglycemia) [68]. A similar study observed an increased insulin secretion by CO (a product of HO-1) [69]. Since type-1 diabetes is coupled with excessive production of inflammatory molecules and ultimately leads to apoptosis, HO-1 induction has been found to have beneficial effects in such conditions [68]. Recently, it has been found that HO-1 induction is responsible for decrease in diabetic neuropathy and in turn increases antinociceptive effects of morphine [70].

Adverse effects associated with HO-1 induction

In spite of such a beneficial mechanism of cytoprotection imparted by HO-1 in diverse stress conditions, its induction has been related to the development of several diseases [71]. In its role of imparting protection to the cells, HO-1 has been observed to increase the survival and suppress the apoptotic pathways in these cells [72]. The increased survival and suppression of apoptosis in these cells may lead to their uncontrolled proliferation and can make them progress towards carcinogenesis, metastasis and other ailments such as neurodystrophic disorders [2].

HO-1 and carcinogenesis

HO-1 acts as a cytoprotective agent in normal tissues exposed to various stimuli. It is induced in response to panoply of stimuli including carcinogens, and its enhanced expression imparts protection to cells. Much data obtained till date report the increased expression of the HO-1 enzyme in tumors in comparison to the surrounding normal tissues. This increased expression of HO-1 was revealed in lymphosarcoma, adenocarcinoma, hepatoma, glioblastoma, melanoma, prostate cancers, Kaposi sarcoma, squamous carcinoma, pancreatic cancer and in brain tumors [2]. Several in vivo studies revealed that animals upon treatment with carcinogens show higher expression of HO-1. For example, HO-1 was seen to be up-regulated in rats which were exposed to alachlor, a known inducer of olfactory tumors [73]. Similarly, the expression of HO-1 was increased in response to dietary *p*-dimethylaminoazobenzene (DAB) inducing hepatic carcinogenesis. Moreover, induction of HO-1 can also take place in response to some chemopreventive compounds. For instance, diallyl sulfide (DAS) increases the expression of HO-1 by increased ROS generation and subsequent increase in activity of transcription factors Nrf2, extracellular signal-regulated kinase (ERK) and p38 kinases. The increase in HO-1 expression by DAB and diallyl sulfide (DAS) was hypothesized to play a key role in the anti-carcinogenic effects of these chemicals [74]. The pancreatic cancer cells treated with gemcitabine or radiation-induced HO-1, while knockdown of HO-1 showed reverse effect inhibiting pancreatic cancer [75]. Induction of HO-1 enzyme genetically or using pharmacological inducers/carcinogens has been suggested to provide a growing environment to tumor cells and confer resistance to chemotherapy and radiotherapy besides protecting these cells from oxidative stress by its anti-oxidative mechanism [2]. This enhanced survival is most probably due to the anti-apoptotic property of HO-1 and increased angiogenesis [76].

An anti-apoptotic aspect of HO-1 has previously been demonstrated both in in vitro and in vivo models of inflammation and tumors. HO-1 is known to prevent apoptosis by mainly activating p38 kinase pathway. However, in many carcinomas, apoptosis is prevented by the involvement of Akt/protein kinase B pathway [77]. One more study has shown that overexpression of HO-1 protected the renal cancer cells from apoptosis induced by rapamycin and sorafenib and helped the tumor cells grow by blocking their apoptotic and autophagic pathways. In addition, it has been reported that when HO-1 is overexpressed, it increases the expression of Bcl-xL (an anti-apoptotic protein), and decreases the Beclin-1 and LC3B-II expression (autophagic proteins). HO-1 is responsible for the induction of anti-apoptotic protein (Bcl-xL) and decreases the expression of Beclin-1 and LC3B-II (autophagic proteins), however, HO-1 knockdown decreases Bcl-xL expression and markedly enhances LC3B-II [78]. In addition, it has been observed that HO-1 induction does not always protect the cells against apoptosis as was thought earlier. A study showed that HO-1 was not able to prevent chemotherapy-induced apoptosis in breast carcinoma model [79].

Further, several studies evidently showed that HO-1 also plays a key role in angiogenesis. Angiogenesis is an essential process for the sustained growth and invasion of solid tumors. In cultured endothelial cells, elevated HO-1 levels have been shown to be involved in the up-regulation of vascular endothelial growth factor (VEGF) and VEGF receptors increased proliferation and migration of endothelial cell and promoted angiogenesis [80]. It has also been seen that when HO-1 was transfected in severe combined immune deficient mice, it enhanced the development of pancreatic tumor via the stimulation of angiogenesis. On the other hand, stannous

mesoporphyrin, the inhibitor of HO-1, transiently delayed the growth of the tumor. HO-1 inhibition is an emerging target to fight against cancer [2]. For instance, in the chronic myeloid leukemia-derived cell line K562, Gleevec-induced apoptosis was counteracted via HO-1 overexpression [81]. The effectiveness of such treatments has also been confirmed in in vivo models. The adenocarcinomic mice which were treated with photodynamic therapy, regrowth of tumors were observed to a great extent due to the increased expression of HO-1 [82]. Thus, using zinc protoporphyrin IX (ZnPPIX), a specific inhibitor of HO-1, expansion of hepatoma and sarcoma or lung cancer in mice can be suppressed significantly [83]. Since induction of HO-1 expression has been linked with cancer invasion. It has been observed that curcumin induces HO-1 expression and thus attenuates its anti-invasive effect in cancer therapy [84].

The effect of HO-1 on the expression of the cancer critical genes (oncogenes and tumor suppressor genes) would significantly collaborate in unraveling the relation between HO-1 activation and pathogenesis of different diseases. But unfortunately, very little data are available about this matter. However, one report reveals that HO-1 does not affect the telomerase and telomerase reverse transcriptase (TERT), which play a major role in cancer progression by regulating telomerase [85]. Moreover, HO-1 knockdown studies or animal models treated with pharmacologic inhibitors of HO-1 will help in determining the actual effect of HO-1 activity on the progression of different diseases and cancers, and the vice versa, i.e., the effect of these diseases on HO-1 expression.

Earlier studies have linked HO-1 gene (GT)*n* repeat polymorphism with the cancer risk [86]. Shorter (GT) repeats have been linked with the low risk of different human cancers such as esophageal squamous cell carcinoma, lung adenocarcinoma, breast cancer, oral squamous cell carcinoma, gastric adenocarcinoma and malignant mesothelioma [86]. But some reports associate shorter (GT) repeats with higher cancer risk for pancreatic cancer, melanoma and gastric cancer [87, 88].

Neurodystrophic role of HO-1

Under certain conditions, HO-1 induction is responsible for providing neuroprotection (as described above). In a normal brain, HO-1 mRNA and protein expression are limited to few scattered neuroglia and neurons. Induction of HO-1 occurs in response to different stress-causing agents. In Alzheimer disease, overexpression of HO-1 protein occurs in neurons and astrocytes of the hippocampus and cerebral cortex [89]. Similarly, in Parkinson's disease, HO-1 is overexpressed in astrocytes (present in the cerebral cortex) [90]. HO-1 is overexpressed in glial cells present in the vicinity of cerebral infarcts, within multiple sclerosis plaques, contusions and hemorrhages, and in other inflammatory and degenerative CNS disorders [91]. HO-1 hyperactivity (chronic expression) leads to the bioenergetic failure and pathological iron deposition as observed in Parkinson, Alzheimer and various other neurodevelopment diseases, by promoting mitochondrial associated non-transferrin iron sequestration and macroautophagy [92]. Moreover, it has been reported that irreversible neurological injury caused by excessive hyperbilirubinemia in untreated neonatal jaundice children, can be prevented by the introduction of synthetic metalloporphyrins (competitive inhibitors of HO activity) [93]. Metalloporphyrin treatment has been shown to confer neuroprotection in the intracerebral hemorrhage experimental model [94] and is associated with diminished edema formation and tissue necrosis in the focal cerebral ischemia rats [95]. HO-1 has been found to facilitate dopaminergic cell injury following polychlorinated biphenyls exposure, which may be of possible relevance to Parkinson's disease [96]. Moreover, it is suggested that differences in experimental models, therapeutic protocols and species may be responsible for the disparate data concerning the role of HO-1 induction in neurological diseases.

HO-1 and other disorders

It has been reported by Ursu et al. that at later stages of myocarditis, HO-1 is associated with apoptosis of heart muscle cells [97]. Additionally, HO-1 overexpression can lead to muscle damage in in vitro and in vivo models, causing skeletal muscle atrophy. However, the lack of HO-1 considerably attenuates muscle atrophy [98].

Conclusion

A large number of studies have been carried out to delineate the diverse roles of HO-1 in inflammatory, neurodegenerative and other stress conditions. However, the actual role of HO-1 in diverse stresses has not been elucidated yet. Several studies have suggested the beneficial roles of HO-1 in humans, e.g., protect tissues against different stresses. While as others have reported the involvement of HO-1 in disease progression. It seems that HO-1 in an attempt to protect the cells from stress involuntarily leads to several detrimental conditions including neurodegenerative diseases and cancer. Thus, HO-1 induction in diverse stress conditions seems to be a necessary evil. So, there is a need to search for the link between the HO-1 and the candidate genes (such as oncogenes and tumor suppressor genes in cancers) involved in various diseases to identify the actual role of HO-1. This will significantly collaborate in unraveling the relation between HO-1 activation and etiology of such diseases. Furthermore, it will eventually help in making

HO-1 a potential therapeutic target for the amelioration of various stress-related diseases. In conclusion, unraveling the crosstalk between HO-1 and different candidate genes involved in diverse diseases will facilitate to comprehend the exact role of HO-1 in different diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that no competing interests exist.

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