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Forum Editorial

Changing Faces of Heme Oxygenases

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Determination of the mechanisms of heme degradation, the main function of heme oxygenases (HOs), dominated researchers' attitudes during the first 30 years since the enzyme discovery in 1968 (40). However, the last 10 to 15 years have provided a plethora of evidence indicating other roles of HOs and their products (for reviews, see 35, 37). The number of publications on HOs is steadily increasing every year; however, we are still far from a complete understanding of this pathway. This issue of *Antioxidants & Redox Signaling*, containing the special Forum on Heme Oxygenases, tries to summarize and extend our knowledge, addressing some, but of course not all aspects of this interesting system.

The role of HO-1 in protection against toxicity of free heme and sequestration of liberated iron are discussed in the review article by Balla and co-workers (3). The authors stress that the role of HO-1 in endothelium is of particular importance, as of all sites in the body, endothelium may be at the greatest risk of exposure to heme. This significance is particularly highlighted by the clinical feature of the sole known human case of HO-1 deficiency, which was characterized by extensive damage of the endothelium and early signs of the development of atherosclerosis. The authors conclude that induction of HO-1, and particularly ferritin, in response to iron liberated from the porphyrin ring is critical to the survival and function of the vascular endothelium and its adaptation to life in an extraordinarily iron-rich environment.

It is quite well known that the final outcome of HO-1 activity can be different in various cells types. Thus, HO-1 protects endothelial cells not only against heme (1) but also from different inflammatory mediators, preventing their apoptosis and stimulating proliferation (for reviews, see 35, 37), whereas the same enzyme can inhibit the proliferation of vascular smooth muscle cells (31). Successful use of such outcomes of HO-1 activity can thus depend on the development of efficient tools for HO-1 overexpression in selected cell types. This approach is the subject of the original communication by Nader Abraham's group (2), describing the strategy of construction and application of an adenoviral vector harboring HO-1 under the control of VE-cadherin promoter (2). This promoter drives specifically the expression of HO-1 to endothelial but not to vascular smooth muscle cells, protecting the previous one against the hyperglycemia-induced stress, a situation with relevance to diabetic conditions.

Numerous protective aspects of HO-1 also are highlighted in the review by Ryter *et al*. (33). The authors summarize recent findings on the function of HO-1, mostly in the respiratory system, explaining its possible role in progression of various diseases and their potential therapy. The review concentrates on carbon monoxide, discussing previous and recent discoveries. Of particular interest are the observations from the same group, showing that CO differentially regulates Toll-like receptor (TLR)–dependent signaling in macrophages by inhibiting translocation of TLR4 (but not TLR-3) to lipid rafts through suppression of NADPH-oxidase–dependent ROS generation (27).

Besides HO-1, HO-2, known as a constitutive enzyme, appears to play a crucial role in respiratory system and many other organs. The functions and interrelations of those HO isoforms are addressed in the review by Shibahara *et al*. (34). The expression of HO-1 and HO-2 can be inducible or repressible, depending on cell types or cellular microenvironment. Hypoxia, a decrease in oxygen concentration, appears to play a different, but not always properly recognized role, as it is often forgotten that in several human cell types, mainly endothelial cells, hypoxia represses HO-1 expression. The same concerns HO-2 in HeLa cells, whereas in other human cells, the HO-1 can be induced on hypoxia treatment (34). The authors also indicate that HO-1 and HO-2 play separate physiologic roles. HO-2 appears to be a potential O_2 sensor (34, 43). Interestingly, the data from HO-$2^{-/-}$ mice, which manifest mild hypoxemia but do not exhibit the remodeling of the small arteries, suggest that targeting of HO-2 by specific inhibitors may be helpful in treatment of pulmonary hypertension. The authors also highlight several interesting aspects of the expression of those two genes, such as, in case of HO-2, the common promoter with HSCARG, a gene of unknown function, or in case of HO-1, the microsatellite promoter polymorphism.

Moreover, HO-1 and its byproducts can also play a "non-canonic" role in physiologic processes, in a way not necessarily, or at least not directly related to protection against oxidative

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stress (Table 1). Thus, the role of HO-1 in the process of blood vessel formation has been revealed, indicating that the enzyme is a modulator of the activity of several growth factors. Among them is the vascular endothelial growth factor-A (VEGF-A), the major mediator of vasculogenesis and angiogenesis (5, 11). Additionally, recently studies showed that HO-1 can be linked to the action of stromal-derived factor-1 (SDF-1), a crucial chemokine responsible for attraction of progenitor cells to the site of ischemia (9). Discussing the involvement of HO-1 in the activity of growth factors, Nathalie Hill-Kapturczak *et al.* (15) review the involvement of HO-1 in the effect of the transforming growth factors family, hepatocyte growth factor/scatter factor, platelet-derived growth factor, fibroblast growth factor, and nerve growth factors. Induction of HO-1 expression by those cytokines, although apparently not by all of them (*e.g*., the bone morphogenetic protein-7 is ineffective) indicates that growth factors and HO-1 are intimately related. The authors suggest that HO-1 induction may be an adaptive response providing a balance for the effects of growth factors; however, those complex interactions have not been yet completely elucidated (15). Further studies should demonstrate the detailed mechanisms of induction of HO-1 by different growth factors. Some of them appear to be more potent than the others, and the cell-specific effects also apply. The underlying cause of such differences remains to be established (*e.g.*, whether it is dependent on the amount of reactive oxygen species induced by different growth factors).

Among the HO-1 byproducts, CO appears to be a crucial mediator of VEGF or SDF-1 activity. Recognition of this function, analogous and most probably complementary to nitric oxide, conveying the effects of growth factors in endothelial cells (6, 12) creates a niche for the potential therapeutic application of this molecule, particularly by the chemicals able to release CO (so-called CORMs: carbon monoxide–releasing molecules) (14).

Elaboration on the potential clinical usefulness of CORMs is a subject of the review by Desmard *et al.* (10). The authors highlight the significance of coordinated response and effects by all the byproducts of HO/CO/biliverdin pathway and the role of various targets of CO, which comprise not only guanylyl cyclase and potassium channels, but also NADPH oxidase, cytochrome oxidase, mitochondrial complexes, and nitric oxide synthase. Interestingly, CO liberated at low-micromolar concentrations from CORM can inhibit NADPH oxidase activity, decreasing superoxide production (39). Conversely, CO, like NO, increases mitochondrial H_2O_2 generation, which, as Desmard *et al*. (10) suggest, may explain the antiproliferative effect of CORMs (10). HO-1 can also degrade the heme necessary for HO-1 activity localized in mitochondria, and the authors speculate that CO decreases NO-dependent inhibition of O_2 uptake and contributes to clearing NO without eliciting excessive $O_2^{-\cdot}$ and $ONOO^-$ formation. The authors convey the message that many heme and metal-containing proteins involved in heme and redox signaling and inflammation are the targets of CO, opening new physiologic, pathophysiologic, and pharmacologic perspectives (10). They also stress that much more attention should be given to the spatial and temporal distribution of CO, rather than arguing about the potency and ab-

Table 1. Summary of the "Non-Canonical" Properties and Functions of Heme Oxygenase Pathway

	HO-1	*HO-2*	*BVR*
Cellular localization	Caveoli, mitochondria Cell membrane? Nucleus	Caveoli, mitochondria Cell membrane?	Caveoli, mitochondria Cell membrane? Nucleus
Functions	Transcription factor	Oxygen sensor	bZIP transcription factor
	Mediator of the activity of growth factors: role in vasculogenesis and angiogenesis		Dual specific protein kinase
	Mediator of the activity of drugs: statins, rapamycin, probucol, others?		
	Chemoprevention		
	Regulation of reactive oxygen species production in mitochondria		
	Iron transport/removal		

The "non-canonical" functions and properties are defined as those that are not directly linked to the heme removal. However, some of them, such as protection against oxidative stress might result from metabolism of small amounts of intracellular heme, and hence involve also the action of the HO byproducts. Some of the non-canonical properties are rather not linked to the heme degradation, and are exerted by the HO or BVR proteins itself.

solute amounts of gas produced in a given condition or microenvironment (10).

Importantly, HO-1 and its byproducts arise also as the crucial mediators preventing the development of immune reactions, a property of significance in the attenuation of graft rejection (36). In this issue, the protective role of biliverdin/bilirubin is discussed in the review by Ollinger *et al*. (29), summarizing accumulating evidence indicating that those products of HO-1 activity can mediate the protective effect in ischemia/reperfusion injury and organ transplantation. The authors suggest that it might be reasonable to test those natural, but highly potent protective molecules in clinical transplantation.

The issue of transplantation and immune response also is addressed in the original research communication by Kotsch *et al.* (20). Induction of HO-1 by cobalt protoporphyrin treatment or increasing organ CO concentration by feeding of rats with methylene chloride reduced the mRNA levels of immunoproteasomes, MHC class II expression, and CO-stimulating molecules in the spleen of recipients of kidney transplant, suggesting diminished migration and activation of donor dendritic cells. Therefore, as Kotsch *et al.* propose, such a strategy can be considered a prevention of prolonged cold-induced ischemia (20). The data are in line with the recently published observations indicating that induction of HO-1 resulted in an inhibition of DC maturation (7). However, we have to be aware that CoPPIX used to induce HO-1 expression can exert its effect independent of HO-1 (24); hence the real involvement of HO-1 in inhibition of dendritic cell maturation still remains rather an open question.

The link of HO-1 induction to the protective mechanisms of drugs has been also recently demonstrated, and those interactions, of high clinical importance, are the subject of the review by Stocker *et al.* (22). Although the expression of HO-1 in most tissues is low, a large number of clinical and experimental pharmacologic compounds have been demonstrated to induce HO-1. This includes statins (21), rapamycin (41), and probucol (44). However, in the editor's opinion, although very interesting, and potentially clinically applicable, the real contribution of HO-1 to drug effectiveness requires further investigation, as it might be overemphasized. The effect may not be a general phenomenon and can be linked to the stress induced by the (too) high concentrations of the drugs used (22, 25).

Nevertheless, the induction of HO-1 by numerous chemicals is a reality, and of particular interest are those known to exert this effect *via* the Nrf2 transcription factor, probably a main target of various chemopreventive strategies (32).

The link between Nrf2 and HO-1 expression is discussed in two original communications. In the first one, So-Hyun Park *et al*. (30) demonstrate that Nrf2-mediated HO-1 induction confers an adaptive survival response to neurotoxin [*i.e*., tetrahydropapaveroline-induced oxidative cell death of PC12 neuroblastoma cells]. This discovery may be potentially exploited in consideration of a chemopreventive strategy against parkinsonism and other neurodegenerative diseases. In a second study, Eun-Joo Joung *et al.* (16) describe the Nrf2-2–mediated effect of capsaicin, a pungent ingredient of red pepper. The results suggest that besides induction of HO-1 expression in HepG2 cells, which may protect the cells against oxidative stress, the reactive quinone metabolites of capsaicin may bind covalently to NAD(P)H/quinone oxidoreductase and thereby inhibit its activity responsible for the production of reactive oxygen species. However, to play a "devil's advocate" role again, we have to consider the limitation of such studies, as the data are lacking, or are limited, on the bioavailability and serum and tissue concentrations of many compounds considered for chemopreventive strategies.

Finally, the other noncanonic properties of HO-1 have been recently revealed (Table 1). First, the initial localization of the enzyme in the endoplasmic reticulum appears to be not the only place where one can expect HO-1 to be active. Recent data indicate that HO-1 is also present in or close to the cellular membrane, where it was found in the caveoli (18), the small vesicles aspiring to the role of crucial players in the interactions between the extracellular environment and the cytoplasm. It might be interesting to investigate whether this localization of HO-1 can be somehow related to the once-described, but not very much investigated role of HO-1 as a part of cellular pump, extruding iron from the cell (4). Of interest in this context are the observations by Choi's group (18) discussed in the review by Ryter *et al*. (33) showing that caveolin-1 serves an intermediate role in the antiproliferative effect of CO in vascular smooth muscle cells (see Fig. 7 in ref. 33). Finally, the nuclear localization of the HO-1 protein was recently revealed, pointing to the role of HO-1 protein as the potential transcription factor (23).

Interestingly, HO-1, as well as its constitutive counterpart, HO-2, appears to localize also to the mitochondria (8), and this placement, a logical one, links HO-1 to the site of potential generation of large amounts of reactive oxygen species. This localization of HO-1 can be of significance in the interaction between CO and nitric oxide synthase or mitochondrial cytochrome *c* oxidase, discussed in the review by Desmard *et al.* (10).

However, the most surprising behavior can be ascribed to biliverdin reductase (BVR), an enzyme catalyzing the reduction of biliverdin IXα. First, the dual pH/cofactor-dependent profile recognizes the enzyme as the unique one. Additionally, BVR functions in the insulin receptor/insulin growth factor-1–controlled regulation of the MAPK and PI3K cascades in linkage with the protein kinase C enzymes. Moreover, BVR regulates gene expression by functioning as a bZIP (basic leucine zipper) transcription factor. Those atypical aspects of BVR are addressed in a comprehensive overview by Mahin Maines (26), who states that the emergence of those features underscores the critical input of BVR in the response of intracellular pathways to the external environment.

The stick always has two ends. The HO-1, and maybe BVR, protective activities, beneficial for the cells, may in the end turn against the organism. The best example is of course the tumor, and it is not surprising that the data showing the salutary functions of HO-1 for tumor cells start to accumulate. The protection against oxidative stress (28, 42), enhancement of neoplastic cell proliferation (42), stimulation of tumor growth by induction of angiogenesis (38, 42), and finally attenuation of the effectiveness of anticancer therapy (13, 19, 28) can result in the enhancement of tumor growth at the expense of organisms, and finally even death. Such a potentially detrimental involvement of HO-1 is the subject of the review by Jozkowicz *et al*. (17), trying to elucidate the apparently false "friendship" appearance of HO-1.

The authors of the Forum did their best to provide the current state-of-the art view of the function of HOs and BVR in

several major organs. However, the issue did not aim and was not intended to exhaust all the aspects of the manifold attributes of those interesting enzymes. Nevertheless, we do hope that the texts delivered in this issue will be a good supplement to the plethora of very recent information that will be presented during the 5th Heme Oxygenases Congress, to be held in Krakow, Poland, from September 5 to 9, 2007.

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