Heme oxygenase-1 as a therapeutic target in inflammatory disorders of the gastrointestinal tract

Vijith Vijayan, Sebastian Mueller, Eveline Baumgart-Vogt, Stephan Immenschuh

Abstract
Heme oxygenase (HO)-1 is the inducible isoform of the first and rate-limiting enzyme of heme degradation. HO-1 not only protects against oxidative stress and apoptosis, but has received a great deal of attention in recent years because of its potent anti-inflammatory functions. Studies with HO-1 knockout animal models have led to major advances in the understanding of how HO-1 might regulate inflammatory immune responses, although little is known on the underlying mechanisms. Due to its beneficial effects the targeted induction of this enzyme is considered to have major therapeutic potential for the treatment of inflammatory disorders. This review discusses current knowledge on the mechanisms that mediate anti-inflammatory protection by HO-1. More specifically, the article deals with the role of HO-1 in the pathophysiology of viral hepatitis, inflammatory bowel disease, and pancreatitis. The effects of specific HO-1 modulation as a potential therapeutic strategy in experimental cell culture and animal models of these gastrointestinal disorders are summarized. In conclusion, targeted regulation of HO-1 holds major promise for future clinical interventions in inflammatory diseases of the gastrointestinal tract.

Key words: Antioxidant; Heme oxygenase; Hepatitis; Immunity; Inflammation; Inflammatory bowel disease; Oxidative stress; Pancreatitis

INTRODUCTION
Heme oxygenase (HO), which was initially described more than 40 years ago, enzymatically degrades heme and produces equimolar amounts of carbon monoxide (CO), biliverdin, and iron[1] (Figure 1). In a coupled reaction, biliverdin is converted into bilirubin (BR) via biliverdin reductase[2]. Two distinct isozymes of HO, HO-1 and HO-2, have been identified and represent the products of two different genes with distinct tissue- and cell-specific expression patterns[3-5]. The constitutive isoform HO-2 is preferentially expressed in brain and testis[6], and is essentially not regulated by metabolic or receptor-mediated

stimuli[26,7]. In contrast, the inducible HO isozyme, HO-1, which exhibits low basal expression levels in most cells and tissues, is markedly upregulated not only by its substrate heme, but also by other oxidative stress stimuli, such as UV-light and lipopolysaccharide (LPS) or directly by reactive oxygen species, such as hydrogen peroxide. In addition, heavy metals, sulfhydryl-reactive reagents, and hypoxia are potent inducers of HO-1[8-10]. Thus, although HO-1 does not directly catalyze an antioxidant reaction, its induction is generally considered an adaptive cytoprotective response against the toxicity of oxidative stress[11-13]. In the current review, we focus our attention on recent findings that show the emerging anti-inflammatory and immunomodulatory role of HO-1 and its products. In particular, we highlight recent advances in the understanding how HO-1 might modulate the inflammatory immune response and the potential role of HO-1 for therapeutic applications in inflammatory conditions of various organs in the gastrointestinal tract.

HO-1 GENE DEFICIENCY CAUSES PROINFLAMMATORY PHENOTYPICAL ALTERATIONS

A potential link between HO-1 and inflammatory disease has been shown by Willis et al[14] in an animal model of carragenin-induced pleurisy, in which specific upregulation of HO enzyme activity attenuated a complement-dependent inflammation. Mice that are deficient for HO-1 not only develop chronic inflammation, but are also highly vulnerable to experimental sepsis induced by the classical proinflammatory mediator endotoxin[15]. In addition, innate and adaptive immune reactions are severely affected in these knockout mice[16-18]. In contrast, HO-2 knockout mice appear to have an intact immune regulation, but exhibit defects in their central and autonomous nervous system[19]. The phenotype of the only known human case of genetic HO-1 deficiency is very similar to that observed in HO-1 knockout mice. This HO-1 deficient patient, a Japanese boy who died at the age of six years, was initially diagnosed with anemia and a chronic inflammatory disorder[20,21].

ANTI-INFLAMMATORY EFFECTS OF HO-1 IN MONONUCLEAR PHAGOCYTES AND ENDOTHELIAL CELLS

Although HO-1 is expressed in all tissues and cells, the immunomodulatory functions of HO-1 appear to be primarily dependent on HO-1 functions in mononuclear phagocytes and endothelial cells. In the following, we describe pertinent findings that illustrate the anti-inflammatory role of HO-1 in these two cell types.

Mononuclear phagocytes
Mononuclear phagocytes, such as monocytes and macrophages, are cells with a common bone marrow lineage and have versatile functions in the innate and adaptive immune system[22-25]. As an example, macrophages ingest and kill invading microorganisms as a first line of defence and are activated by various immunological stimuli, such as microbial products or cytokines. In response to these stimuli, macrophages are able to initiate and enhance the inflammatory immune response[26]. It has been known for many years that tissue macrophages, such as Kupffer cells and spleen macrophages, are cell types in which HO-1 is highly expressed under normal conditions[27,28]. Several studies have been performed with cultured mononuclear cells from rodents. Here, HO-1 is upregulated in response to LPS[27-29], which attenuates the expression of various proinflammatory genes, such as cyclooxygenase-2, tumor necrosis factor-α, interleukin (IL)-1, and IL-6[30,31]. The cell-specific antiinflammatory function of HO-1 in mononuclear phagocytes was recently confirmed in a conditional HO-1 knockout mouse model. The cell-specific lack of HO-1 in mononuclear cells caused a major defect of interferon-β expression. In addition, a pathological immune response in an experimental infection with Sendai virus and autoimmune encephalomyelitis in these animals was observed[32]. Interestingly, others have shown that HO-1 is also important for the appropriate function of human and mouse dendritic cells. It has been shown that pharmacological induction of HO-1 attenuates maturation and cell-specific functions of dendritic cells[33,34]. Moreover, HO-1 expression in mononuclear cells has been demonstrated to be essential for the functionality of regulatory T cells[17].

Endothelial cells
The endothelium plays a central role in the regulation of inflammatory reactions, because it serves as a barrier between the peripheral blood stream and inflamed tissues. More specifically, endothelial monolayers regulate the recruitment and transmigration of immunologically active blood cells, such as polymorphonuclear leukocytes (neutrophils) or T lymphocytes, to the site of an inflammation[35,36]. Hayashi and colleagues[37] have reported that HO-1 regulates cell-cell interactions between polymorphonuclear leukocytes and endothelial cells. These authors showed in an in vivo rat model that the increased
enzyme activity of HO in the endothelium of microvessels downregulated the adhesion of leukocytes during experimental oxidative stress[57]. Accordingly, others have demonstrated that the activity of endothelial HO-1 specifically modulates leukocyte recruitment into organs with an experimental inflammation[58]. Independently, in a streptozocin-induced rat model of experimental diabetes, overexpression of HO-1 has been shown to attenuate oxidative stress-dependent endothelial cell damage[59]. Similar findings in the endothelium have recently been reported for knockout mice, in which genetic deficiency of HO-1 caused major pathological alterations of the endothelial monolayer[60]. Specifically, endothelial cells from HO-1 deficient mice were shown to be more susceptible to apoptosis and denudation from the extracellular matrix. Moreover, independent groups have shown that antiinflammatory endothelial protection of HO-1 might be mediated via its ability to downregulate the tumor necrosis factor-α-induced expression of various adhesion molecules[41-43]. It is also remarkable that histopathological studies in the autopsy of a human patient with genetic HO-1 deficiency revealed major endothelial cell damage[21]

HOW DOES HO-1 MEDIATE ITS ANTIINFLAMMATORY FUNCTIONS

The mechanisms of how HO-1 may counteract inflammatory reactions are not understood in detail. An accumulating body of evidence, however, indicates that the HO substrate heme is a compound with major proinflammatory properties and that the HO products BR and CO have potent antiinflammatory functions.

Heme as a proinflammatory compound

The tetrapyrrole heme has contradictory biological properties. On the one hand, heme is important for oxygen and mitochondrial electron transport as the prosthetic group of various hemoproteins such as hemoglobin, myoglobin, and cytochromes[44,45]. On the other hand, heme can be toxic as it can cause oxidative stress in its “free” non-protein bound form. The prooxidant properties of heme have been shown in various animal and cell culture models[46,47]. Due to the critical role of intracellular heme levels, enzymatic synthesis and degradation of this compound is tightly controlled[48-52]. More recently, heme has also been recognized to exhibit potent proinflammatory properties[53,54]. As an example, Jeney et al[29] have demonstrated that heme-dependent oxidation of low-density lipoproteins is involved in inflammation-mediated tissue damage. In this report, the proinflammatory effects of heme have also been shown to be correlated with specific clinical conditions, such as atherosclerosis and hemolytic anemia[55]. Independently, others have demonstrated that intravenous administration of heme caused experimental inflammation in vivo with a major influx of leukocytes[56]. Heme-dependent toxicity has also been associated with its proinflammatory effects in an animal model of experimental cerebral malaria, in which heme-dependent detrimental effects were markedly more pronounced in HO-1 knockout mice[53]. Recent findings might shed light on the mechanisms that could be involved in the proinflammatory effects of heme. Figueiredo and colleagues have demonstrated that initiation of heme-dependent inflammation was mediated via specific interaction of heme with the central pattern recognition receptor toll-like receptor-4, in a cell culture model of mononuclear cells and in mice[54]. The role of HO-1 in maintaining intracellular heme homeostasis has been reviewed elsewhere[54,47,48,51].

Bilirubin

The role of bilirubin (BR) as a beneficial compound with potent antioxidant and antiinflammatory effects has only been appreciated in recent years[55,56]. Protection against an experimental inflammation has been shown for HO-derived BR in an animal model[57]. Moreover, it has been observed in a murine asthma model that BR specifically reduces leukocyte transmigration to the site of an experimental inflammation via interaction with the adhesion molecule vascular cell adhesion molecule-1[58]. More recently, it has been reported in a mouse model of sepsis that a single bolus of BR markedly blocked the toxicity of endotoxin[59]. Epidemiological studies have indicated that moderately increased concentrations of serum BR (e.g. in Gilbert’s disease) are associated with a lower risk of developing cardiovascular disease[59,60] and colorectal carcinoma[61]. In conclusion, the generation of BR by HO-1 might, in part, explain the antiinflammatory effects of this enzyme.

CO

Although CO is generally considered a toxic gas, various physiological functions of CO as a major signaling molecule have been recognized in recent years[53,55]. In particular, HO-1-derived CO has been shown to be involved in the regulation of apoptosis, neurotransmission, coagulation, vasodilation, and inflammation. In a pioneering report on the potential protective effects of this gas, administration of exogenous CO has been shown to block the LPS-induced production of proinflammatory cytokines via modulation of p38 MAP kinase[29]. Similar to the signaling gas NO, CO upregulates the production of cGMP via activation of soluble guanyl cyclase. This mechanism has also been implicated in other functions of CO, such as vasodilation and blockage of smooth muscle cell proliferation. A remarkable development with major potential for future therapeutic applications has been the introduction of CO-releasing molecules (CORMs). CORMs are compounds that can be administered intravenously and are intended to deliver CO to its target site without the toxicity of gaseous CO[62]. Further details on CO and CORMs are given in specific reviews[53,55,56].

HO-derived iron

Iron, as the third product of HO, is an essential com-
In Mechanism of protection by HO-1  

In Homing of hemin-treated macrophages in pancreas before onset of infections  

A lack of appropriate animal and cell culture models to study these infections has prevented by viral HBV and HCV infections has been prevented by their potential therapeutic use. Research on hepatitis B and C, and is a major cause of liver cirrhosis and end-stage liver disease worldwide. These disorders are characterized by chronic self-perpetuating inflammation of the liver for at least six months. For example, chronic hepatitis C virus (HCV) infection affects 4 million US citizens, a third of whom will progress to liver cirrhosis and primary hepatocellular carcinoma if left untreated. Treatment with interferon and ribavirin is effective in only 50% of patients, because many patients either have contraindications to these therapies or have failed to respond to this treatment, indicating a need for alternative or supplementary therapeutic strategies. In the following, we will focus on links between HO-1 and chronic viral hepatitis and their potential therapeutic use. Research on hepatitis B virus (HBV) and HCV infections has been prevented by a lack of appropriate animal and cell culture models to study these infections.  

As regards HO-1 and HBV infection, Protzer and colleagues have reported that HO-1 has antiviral activity in a transgenic mouse model of chronic HBV infection. In this animal model, specific induction of HO-1 by cobalt-protoporphyrin-IX significantly reduced the levels of the viral HBV core protein. Moreover, these authors have shown that the antiviral effects of HO-1 are mediated via reduction of HBV core protein stability in cell cultures of stably transfected hepatoma cells.  

Several reports suggest that HO-1 might serve as a specific therapeutic target for the treatment of chronic HCV infection, although the results are somewhat contradictory. On the one hand, Schmidt and colleagues have presented evidence that HCV specifically downregulates gene expression of HO-1, but not that of other antioxidant genes, such as manganese superoxide dismutase and catalase. In cell cultures of hepatoma cells, inhibition of HO-1 by HCV appeared to be specifically regulated via the HCV-core protein. Moreover, these authors have shown that the antiviral effects of HO-1 are mediated via reduction of HBV core protein stability in cell cultures of stably transfected hepatoma cells.  

Table 1 HO-1 and inflammatory disorders of the gastrointestinal tract  

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HO: Heme oxygenase; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

TARGETING HO-1 IN INFLAMMATORY DISORDERS OF THE GASTROINTESTINAL TRACT  

**HO-1 and chronic viral hepatitis**  

Chronic viral hepatitis mainly consists of viral hepatitis B and C, and is a major cause of liver cirrhosis and end-stage liver disease worldwide. These disorders are characterized by chronic self-perpetuating inflammation of the liver for at least six months. For example, chronic hepatitis C virus (HCV) infection affects 4 million US citizens, a third of whom will progress to liver cirrhosis and primary hepatocellular carcinoma if left untreated. Treatment with interferon and ribavirin is effective in only 50% of patients, because many patients either have contraindications to these therapies or have failed to respond to this treatment, indicating a need for alternative or supplementary therapeutic strategies. In the following, we will focus on links between HO-1 and chronic viral hepatitis and their potential therapeutic use. Research on hepatitis B virus (HBV) and HCV infections has been prevented by a lack of appropriate animal and cell culture models to study these infections.  

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In contrast, findings from independent reports have indicated that targeted overexpression of HO-1 had antiviral effects on HCV replication (Table 1). The group of Bonkovsky has demonstrated that upregulation of HO-1 by a pharmacological approach or, more recently, by a microRNA-based strategy repressed HCV replication in human Huh-7 hepatoma cells. Accordingly, Zhu et al. have shown that targeted overexpression of HO-1 led to a significant inhibition of HCV replication without affecting other parameters of cell viability in human hepatoma cells, which stably replicate subgenomic selectable HCV RNAs. These studies have recently been extended by others, who have shown that the HO-1 product biliverdin interfered with HCV replication via direct modulation of the antiviral interferon-α response in two human hepatoma replicon cell lines (Table 1).  

Due to the limited success rate of current therapies for chronic viral hepatitis, it is conceivable that targeted modulation of HO-1 might be an innovative comple-
mentary strategy for the treatment of these infectious diseases.

**HO-1 and inflammatory bowel disease**

Inflammatory bowel disease (IBD) is a group of chronic inflammatory disorders, which is primarily represented by ulcerative colitis and Crohn’s disease. The etiology of IBD is not well understood and a complex interplay of genetic, immunological and environmental factors appears to play a role in the initiation and perpetuation of IBD. The onset of IBD is characterized by an autoimmune inflammatory reaction that causes excessive production of pro-inflammatory cytokines and reactive oxygen species, which in turn damage the intestinal mucosa. A number of experimental animal models of IBD have been established, in which IBD develops either spontaneously, such as in various knockout mouse models, or after treatment with specific chemical compounds, such as trinitrobenzene sulfonic acid (TNSA). These models are widely used to investigate potential therapeutic strategies for the treatment of IBD. HO-1 regulation has been studied in a variety of these animal models and in biopsies from human IBD patients.

In a trinitrobenzene sulfonic acid-induced model of experimental colitis, it has been demonstrated that HO-1 is prominently upregulated in various cell types of the inflamed colon. These findings correspond with observations from an independent study, in which increased HO-1 expression has been observed in mucosa biopsies of a murine colitis model. Importantly, in this study, HO-1 expression has also been shown to increase in inflamed mucosa of human IBD patients for a Japanese population. Indirect evidence that HO-1 might play a role in the pathogenesis of IBD has been demonstrated in knockout mice for the Nrf2 gene, which is the major transcriptional regulator of HO-1. Nrf2-deficient mice were more susceptible to develop an experimental colitis in response to dextran sodium sulphate when compared with their wild-type counterparts.

As regards the potential therapeutic role of HO-1 in IBD, important insights have been presented in independent reports on HO products (Table 1). In a dextran sodium sulphate-induced colitis model, HO-1-dependent protection against inflammation has been attributed to the beneficial effects of biliverdin. By contrast, others have indicated that CO might provide anti-inflammatory protection in mice with genetic IL-10 deficiency, which develop a chronic colitis-like disease. In these mice it is also shown that the immunosuppressive effects of CO were recapitulated by pharmacological induction of HO-1. Interestingly, upregulation of HO-1 might also play a role in the anti-inflammatory protective effects of some established current standard therapies of IBD. As an example, Horváth et al. have shown that 5-amino salicylic acid (5-ASA), which is one of the pharmacological standard therapies of IBD, might, at least in part, mediate its anti-inflammatory effects via upregulation of HO-1 in a trinitrobenzene sulfonic acid-induced rat colitis model. In addition, others have demonstrated that the fungal metabolite gliotoxin and the HO-1 substrate heme mediate anti-inflammatory effects in independent experimental colitis models via specific induction of HO-1, respectively (Table 1).

Finally, it is important to point out that targeted HO-1 induction does not provide anti-inflammatory protection in an experimental animal model of dextran sulphate sodium-induced colitis, when HO-1 was induced after the onset of IBD. Therefore, it seems questionable whether HO-1 induction is useful for treatment of established IBD, but rather might be useful as a preventive measure.

**HO-1 and pancreatitis**

Pancreatitis is an inflammatory disorder that is clinically categorized into acute and chronic pancreatitis. The clinical stages of pancreatitis range from a transient self-limiting inflammatory reaction to a fulminant disease with necrotic lesions. Severe acute pancreatitis, which might have multiple local and systemic complications, is associated with high mortality. In general, acute pancreatitis is caused by alcohol abuse and gallstones. More recently, however, genetics and obesity have been identified as independent risk factors. The pathogenesis of pancreatitis is not well understood, but it is known that proinflammatory pancreas-independent factors, such as exposure to endotoxin, can trigger the onset of the disease. Oxidative stress has repeatedly been implicated in the pathogenesis of pancreatitis. Although the exact role of oxidative stress during the course of the disease is not well understood, antioxidant enzymes and vitamins have been shown to improve the clinical consequences of pancreatitis. Other therapeutic strategies for the treatment of pancreatitis include inactivation of pancreatic enzymes and blockade of platelet factor activating receptor.

HO-1 is upregulated in animal models of experimental pancreatitis in a cell-specific manner. In particular, it has been demonstrated that HO-1 gene expression in the inflamed pancreas is primarily upregulated in peripheral macrophages, which migrate into areas of inflammation (Table 1). In the latter report, the authors have also asked whether HO-1 induction might protect against pancreatitis. The major finding of this study, in which experimental pancreatitis was induced with a choline-deficient diet, indicated that administration of heme decreased pancreatitis-associated lethality in mice. Moreover, administration of heme increased the pancreatic tissue secretion of chemo-kines, which was responsible for the infiltration of HO-1 expressing peritoneal macrophages into the pancreas. It is important to note, however, that heme-dependent HO-1 induction after the onset of pancreatitis failed to reduce the severity of the disease. This finding is similar to what has been observed in IBD, as mentioned above. Thus, although HO-1 induction might not be useful for the treatment of established pancreatitis, it might help to prevent the onset of pancreatitis in a clinical setting, in which pancreatitis is likely to develop. In a model of pancreas transplantation, in which pancreatitis develops as a consequence...
of ischemia-reperfusion injury, pharmacological induction of HO-1 has been shown to be protective against pancreatitis\(^{[102]}\) (Table 1). Similar observations have also been reported in an independent study, in which pretreatment with cobalt-protoporphyrin-IX prevented the microcirculatory dysfunction after pancreas ischemia–reperfusion injury in rats\(^{[103]}\). More recently, the CO donor CORM-2 has been shown to protect against acute pancreatitis in rats\(^{[104]}\). Finally, specific induction of HO-1 might also be applicable for treatment of chronic pancreatitis. In a recent report, Schwer et al\(^{[105]}\) have shown that HO-1 induction by curcumin inhibited pancreatic stellate cell proliferation, which plays a major role in the pathogenesis of pancreatic fibrosis in chronic pancreatitis. This protection was abolished by blockage of HO activity, either by an enzyme inhibitor or by knockdown of HO-1 with a specific siRNA (Table 1).

**CONCLUSION**

Targeted overexpression of HO-1 has major potential for the treatment of inflammatory disorders of the gastrointestinal tract. Current knowledge on the applications of HO-1 as a therapeutic target, however, still seems precarious and critical questions remain to be answered before clinical interventions might be available.

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