

Heme oxygenase-1 system and gastrointestinal tumors

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Abstract

Heme oxygenase-1 (HO-1) system catabolizes heme into three products: carbon monoxide, biliverdin/bilirubin and free iron. It is involved in many physiological and pathophysiological processes. A great deal of data has demonstrated the roles of HO-1 in the formation, growth and metastasis of tumors. The interest in this system by investigators involved in gastrointestinal tumors is fairly recent, and few papers on HO-1 have touched upon this subject. This review focuses on the current understanding of the physiological significance of HO-1 induction and its possible roles in the gastrointestinal tumors studied to date. The implications for possible therapeutic manipulation of HO-1 in gastrointestinal tumors are also discussed.

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INTRODUCTION

Heme oxygenase (HO) plays an important role in regulating the intracellular heme level by cleaving heme into carbon monoxide (CO), biliverdin and free iron^[1]. Three HO isoforms have been identified to date: HO-1, HO-2, and HO-3, among which the isoforms 1 and 2 are the best known. HO-2 is constitutively and most highly expressed in neuronal tissues contributing to cell homeostasis, whereas HO-1, also referred to as heat shock protein-32 (Hsp32), is an inducible enzyme and relatively lowly expressed in most tissues^[2]. HO-3, which is described in the rat brain, has no activity and is not expressed in humans^[3].

HO-1 and HO-2 are different gene products. Unlike the constitutively expressed HO-2, HO-1 is exquisitely sensitive, not only to heavy metals^[4], but to all kinds of stimuli and agents that cause oxidative stress and pathological conditions, including ischemia^[5], hemorrhagic shock^[6], heat shock^[7], hypoxia^[8], UVA radiation^[9], reactive oxygen species (ROS)^[10]. In fact, there is no other enzyme to date that is affected by so many stimuli of diverse nature as HO-1^[2].

HO-1 is involved in many pathophysiological processes, ranging from Alzheimer's disease to cancer. The interest in this system by investigators involved in gas-

gastrointestinal tumors is fairly recent, and few reports on HO-1 have focused on this subject.

HO-DERIVANTS AND THEIR EFFECTS

All products of HO activity are now suspected to be biologically active, in which metabolic pathway is involved in a wide variety of physiological and pathophysiological processes^[11]. Almost all CO produced *in vivo* comes from the degradation of heme by HO. Depending on the cell type, CO can activate one or both key signaling pathways in numerous physiological and pathophysiological conditions (Figure 1). One of the pathways is soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP), which has been implicated in mediating the effects of CO on vascular contractility, the inhibition of smooth muscle proliferation, neurotransmission^[12,13] and preventing apoptosis in endothelial cells^[14] and fibroblasts^[15]. Another one is p38 mitogen-activated protein kinase (MAPK) pathway, through which CO can mediate the anti-inflammatory actions in a large measure^[16-18]. Moreover, Chin *et al.*^[19] recently pointed out that CO has played an additional novel role as a host defense molecule agent against microbes (bactericidal agent).

HO-1 catalyzes the rate-limiting step in heme degradation to biliverdin. Biliverdin is, in turn, converted into bilirubin by biliverdin reductase at the expense of NADPH. Biliverdin and bilirubin are potent antioxidants^[20,21]. Several studies have demonstrated that the administration of biliverdin and/or bilirubin is potently cytoprotective in a variety of pathophysiological events, including ischemia-reperfusion injury, transplant rejection and inflammatory bowel disease^[22-25]. In addition, bilirubin is also known to modulate immune effector functions and suppress inflammatory response^[26].

Fe²⁺, which is also a product of heme degradation, upregulates an iron-transporter pump that removes intracellular Fe²⁺ from the cell^[27] and induces the expression of ferritin, a iron binding protein^[28]. Expression of ferritin is originally reported to protect endothelial cell against oxidant damage *in vitro*^[28]. In addition, over-expression of H-ferritin (heavy chain ferritin) has also been shown to protect cultured endothelial cells from undergoing apoptosis and protect livers from transplant-associated ischemia-reperfusion injury^[29]. Although the roles of the iron and ferritin in the overall cytoprotective effect of HO-1 are not clear, presumably both contribute in a crucial manner to the overall anti-oxidant effect following increased HO-1 expression in a variety of situations^[30].

EXPRESSION OF HO-1 IN GASTROINTESTINAL TUMORS

Expression of HO-1 is usually increased in tumors, compared with surrounding healthy tissues, which was shown in oral squamous cell carcinoma^[31], pancreatic cancer^[32] and hepatoma^[33]. There have been few published reports in gastrointestinal tumors and only one paper to date has investigated HO-1 expression in gastrointestinal tumors.

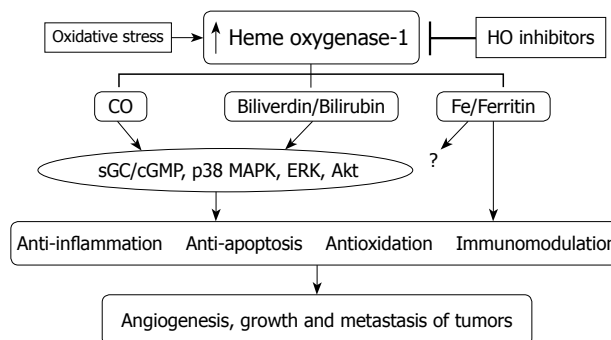


Figure 1 Schematic demonstration of mechanism underlying the biological actions of HO-1 pathway in tumors. HO-1: Heme oxygenase-1; CO: Carbon monoxide; sGC/cGMP: Soluble guanylate cyclase/cyclic guanosine monophosphate; MAPK: Mitogen-activated protein kinase.

The study investigates the expression of HO-1 in human colon tumor. Focal HO-1 expression in colorectal cancer and colonic adenoma was found to be 41.8% (23/55) and 36.8% (7/19), respectively^[34]. Of importance, HO-1 in gastrointestinal tumors can be further upregulated in response to chemotherapy^[35] and photodynamic therapy^[36].

HO-1 PROMOTER POLYMORPHISM

HO-1 is known as an oxidative stress responsive protein that is upregulated by multiple stimuli, which has been proposed to provide an important cellular response that protects cells against oxidative damage. However, humans differ quantitatively in their ability to mount an HO-1 response. The association between the HO-1 genotype and various gastrointestinal tumors has been studied. Lo *et al.*^[37] examined the correlation between the HO-1 gene promoter polymorphism and the clinicopathological characteristics, along with the risk of gastric cancer. Their findings suggest that the long (GT)_n repeat of HO-1 gene promoter was associated with a higher frequency of gastric adenocarcinoma, and the medium (GT)_n repeat might possess a protective effect against gastric adenocarcinoma with a lower frequency of lymphovascular invasion in tumors. Additionally, the (GT)_n-repeat promoter polymorphism was investigated in gastrointestinal stromal tumors (GIST) by Vashist *et al.*^[38]. They found that Short GT_n allele (SGT_n) was significantly associated with metastasis, higher tumor recurrence rates and high-risk GIST. Furthermore, SGT_n allele carriers had significantly shorter disease-free and overall survival^[38]. Moreover, a higher promoter activity genotype of the HO-1 gene was associated with increased risk in women with gastric cancer^[39]. In gastrointestinal tumors, a potential impact of the (GT)_n repeat polymorphism has been demonstrated, which might be considered as a potential prognostic marker to allocate patients to different risk groups and customize therapy and follow-up.

HO-1 AND CYTOPROTECTION AND APOPTOSIS

The gastrointestinal tract is lined by a simple epithelium

that undergoes constant renewal involving cell division, differentiation and cell death, in which HO-1 plays a major role in the regulation of the cell cycle/apoptosis, oxidative stress, inflammation, development of colon cancer^[40]. Many studies have convincingly shown that HO-1 is a cytoprotective and antiapoptotic enzyme in gastrointestinal tumor cells exposed to diverse stimuli (Figure 1). It has been demonstrated that HO-1 is involved in the pathogenesis of human gastric cancer. Antiapoptotic effects of HO-1 in gastric cancer cells are independent of p53 status in a p38 MAPK- and ERK-mediated pathway with elevated caspase inhibitory protein-2 (c-IAP2) and decreased caspase-3 activity^[41], in which nuclear factor- κ B is implicated. The pathway of HO-1 was also investigated in HT29 human colon cancer cells by Park *et al.*^[42]. Another study also demonstrated that HO-1 induction resulted in resistance to apoptosis in a human colon cancer cell line, Caco-2, whose effects were independent of p38, but were mediated *via* Akt pathway^[43]. In a similar study, Kim *et al.*^[44] reported that administration of Zerumbone (ZER) effectively suppressed mouse colon carcinogenesis through multiple modulation of growth, apoptosis and inflammation. Ohyama *et al.*^[45] examined the cytotoxicity of a crude extract from Vitex agnus-castus fruits (Vitex extract) in gastric signet ring carcinoma (KATO-III) cells. They found that cell apoptosis may be attributed to the inhibition of HO-1. It can be supposed that cytoprotective action of HO-1 can be mediated by the following factors: (a) decreased intracellular pro-oxidant levels; (b) increased bilirubin levels; and (c) elevated CO production^[46]. On the contrary, flavonoids- (Vitex extract) induced apoptosis is caused through the induction of HO-1 in human colon carcinoma cell line, COLO 201^[35]. The relationship between HO-1 and apoptosis remains to be clarified.

HO-1 AND TUMOR GROWTH AND METASTASIS

Apart from the cytoprotective action, HO-1 is commonly regarded as a potent proangiogenic enzyme. Angiogenesis is critical not only for tumor growth but also for metastasis. Thus, proangiogenic action of HO-1 may further support tumor progression^[47]. Bussolati *et al.*^[48] reported that vascular endothelial growth factor (VEGF) induced prolonged HO-1 expression and activity in human endothelial cells and HO-1 inhibition abrogated VEGF-driven angiogenesis. Overexpression of HO-1 in pancreatic cancer cells^[49] and melanoma cells^[50] increased the occurrence of metastasis, while inhibition of HO activity completely inhibited the occurrence of metastasis^[49]. In contrast, some authors have demonstrated that inhibition of the HO pathway by zinc deuteroporphyrin 2,4-bis glycol (ZnDPBG) in colon carcinoma had no effect on metastasis to the lung and even increases metastasis to the liver^[51]. Furthermore, the rate of lymphatic tumor invasion was significantly lower in colorectal cancer samples expressing HO-1^[34]. Thus, the mechanism of HO-1 in the metastatic potential of cancer cells is not

recognized and it may depend on the type of cancer or other still not defined factors.

HO-1 AS A POTENTIAL THERAPEUTIC TARGET

Studies of the role of HO-1 seem to be important not only for better understanding of tumor growth regulation but also for clinical practice. HO-1 is often up-regulated in gastrointestinal tumors^[34], its expression is further increased in response to the different types of therapies such as photodynamic therapy^[52,53] and pyrrolidine dithiocarbamate^[54]. Since HO-1 may protect tumor cells against oxidative stress and can be regarded as an enzyme facilitating tumor progression, administration of HO-1 inhibitors might be effective for the treatment of gastrointestinal tumors. It has been demonstrated that pegylated zinc protoporphyrin, a potent HO inhibitor, administered *in vitro* induced apoptosis of human colon carcinoma SW480 cells and inhibited growth of murine colon carcinoma *in vivo*^[55]. However, the growth, invasion and metastasis of tumors are a highly complex and multistep process, the mechanisms responsible for HO-1 in gastrointestinal tumors remain to be elucidated.

CONCLUSION

HO-1 system may play an important role in different pathophysiological conditions, in which pharmacologic modulation of HO-1 system may represent an effective and cooperative strategy to facilitate tumor growth and metastasis, although the exact effects can depend on the type of disease. Therefore, down-regulating the HO-1 system by pharmacological or genetic means will be a new therapeutic approach in the management of gastrointestinal tumors. A comprehensive understanding of the underlying mechanisms for the observed effects of HO-1 and its products will be necessary before their use can be evaluated in clinical applications for the prevention and/or treatment of human diseases such as gastrointestinal tumors.

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