Heme Oxygenase-1 in Cardiovascular Diseases: Molecular Mechanisms and Clinical Perspectives

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Heme oxygenase (HO) catalyzes the rate-limiting step in the oxidative degradation of cellular heme that liberates iron, carbon monoxide (CO), and biliverdin. Two distinct HO isoforms have been identified in mammalian system. Compared to HO-2, which is constitutively expressed, HO-1 is a stress-responsive protein that is highly induced by many agents, including cytokines, endotoxin, heavy metals, nitric oxide and its own substrate heme. In addition to its well-defined role in heme catabolism and erythrocyte turnover, HO-1 also plays an important function in various physiological and pathophysiological states associated with cellular stress. Over the past decade, compelling evidence has revealed that the induction of HO-1 represents an important defensive mechanism against further oxidative injury in tissues and cells following various insults; this occurs by virtue of the anti-inflammatory and antioxidant capacities of CO, biliverdin, and the subsequent metabolite of biliverdin, bilirubin. In line with the findings from the basic research, numerous studies have supported the importance of HO-1 in various clinical diseases, including coronary artery disease, cardiac hypertrophy, diabetes mellitus, ischemic/reperfusion injury, atherosclerosis and cancer. This review provides an overview on the regulation and function of HO-1, ranging from the molecular mechanisms involved to various clinical perspectives. Specifically, there is a focus on the enzyme’s role in various cardiovascular diseases. (Chang Gung Med J 2010;33:13-24)

Key words: heme oxygenase-1, carbon monoxide, bilirubin, clinical perspectives
important cell signaling properties. After the initial report in 1993 showing that CO served as a signaling molecule, CO was implicated in a wide range of cellular responses and physiological/pathophysiological states, which stretch well beyond the initial expectations. Moreover, bilirubin, which is also a byproduct of heme degradation, was found to have important anti-oxidant effects in 1987. In light of these findings, the HO system has attracted considerable interest due to it’s various roles, extending from heme catabolism to cytoprotective defense mechanisms in response to various cellular stresses and diseases. In this review, we provide a comprehensive overview on the molecular mechanisms underlying the regulation and function of HO-1 and its clinical implications. In addition, the therapeutic potential of modulating HO-1 activity in terms of clinical applications will be discussed.

**HO-1 gene identification**

Human erythrocytes live for about 120 days and aged erythrocytes undergo plasma membrane changes that render them susceptible to recognition for phagocytosis in the spleen and liver. The reticuloendothelial system, which is composed of macrophages, plays a key role in the recycling of the senescent erythrocytes and the release of important breakdown products. The heme of the hemoglobin is broken down into iron, CO and biliverdin. The biliverdin is subsequently reduced by biliverdin reductase to bilirubin, which is then bound to albumin, conjugated in the liver, and excreted into the gut. The iron is transferred by transferrin and recycled. In 1968, hemoglobin-heme was first noted to be enzymatically converted to bilirubin by the microsomal fraction from liver, spleen or kidney. This activity is highest in the spleen and can be inhibited by CO. Since this enzymatic activity requires NADPH and oxygen and is strongly inhibited by CO, which is a typical feature of microsomal mixed function oxidases, this enzyme was termed HO. In 1985, using antibody screening, a rat HO cDNA coding for 289 amino acids was cloned and later designated as HO-1. As HO is a microsomal enzyme, it needs to be inserted into the endoplasmic reticulum posttranslationally. The amino acid sequence analysis has revealed that a hydrophobic segment at the carboxyl terminus is essential for HO anchoring to the membrane.

A genetically distinct HO isozyme (HO-2) was subsequently identified. Compared to HO-2, which is constitutively expressed in various tissues and cells, HO-1 is highly induced by many factors, including heavy metals, endotoxin, cytokines, heme, nitric oxide, hypoxia, and UV irradiation. HO-1 expression is highest in the spleen, reticuloendothelial cells of the liver and bone marrow, which are the responsible organs for degrading senescent red blood cells. In other tissues which are not directly responsible for the hemoglobin metabolism, the basal expression of HO-1 is very low but can be rapidly induced upon stimulation. The finding that a vast range of stimuli can induce HO-1 indicates that HO-1 expression is subjected to regulation by many cellular signaling pathways through the multiple response elements present in HO-1 gene promoter.

**HO deficiency**

Mice with a HO-1 null mutation have been shown to develop anemia associated with hepatic and renal iron overload and this contributes to the oxidative tissue injury and chronic inflammation. Moreover, HO-1 deficient mice develop right ventricular infarction after chronic hypoxia exposure and are more susceptible to ischemic and reperfusion injury. The first human case of HO-1 deficiency has also been reported. This patient suffered persistent hemolytic anemia and an abnormal coagulation/fibrinolysis system, which were associated with elevated thrombomodulin and von Willebrand factor, indicating persistent endothelial damage. Likewise, studies on HO-2 deficient mice revealed that these animals exhibit hypoxemia and hypertrophy of the pulmonary venous myocardium and are more susceptible to hyperoxic lung damage, which is associated with increased expression of HO-1. These findings provide strong evidence to support that HO has important functions in normal physiology and pathophysiology, especially with regard to the cardiovascular system.

**Regulation of HO-1 expression**

The mitogen-activated protein kinase (MAPK)-activated signaling pathway was the first recognized as able to mediate the induction of HO-1 by extracellular stimuli. MAPKs belong to evolutionarily conserved serine/threonine protein kinases that regulate multiple cellular functions including prolifera-
tion, apoptosis, differentiation and environmental stimuli responses. The MAPKs are composed of three families, the extracellular signal regulated kinases (ERK1/2), the c-Jun NH2-terminal kinases (JNK), and the p38 MAPKs. Each family consists of several functionally related kinases with distinct activities associated with phosphorylation of their specific downstream targets and transcriptional factors. These diverse effects highlight the complexity of the MAPKs signaling that is implicated in the interaction between extracellular stimuli and transcriptional activation of HO-1 gene. In this context, the molecular details of how the MARKs signaling cascades transduce and lead to the nuclear HO-1 gene transcription are not yet fully dissected. The phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway is also involved in HO-1 regulation. PI3K/Akt can be activated through many growth factors and cytotoxic stimuli. Akt can also directly phosphorylate HO-1 at Ser-188 and modulate its activity. Moreover, other signaling molecules, such as protein kinase C and tyrosine kinase, are also able...
to influence HO-1 expression. Given the complex features of the cell signals and diverse extracellular stimuli involved in the regulation of HO-1 gene expression (Fig. 1), it is envisaged that multiple response elements and diverse transcription factors are involved in HO-1 gene transcriptional activation across various cellular contexts and different cell types. The human HO-1 gene promoter sequence encompasses more than 10 kb and contains a number of regulatory cis-elements, including stress-responsive element, heat shock element, hypoxia responsive element, metal responsive elements, negative regulatory element, cadmium responsive element, CAAT/enhancer binding protein binding site and NF-kB binding site. Numerous studies have revealed the involvement of various transcriptional factors, including AP-1, Nrf2, Bach1, hypoxia-inducible factor-1 (HIF-1) and ATF-2, in the regulation of HO-1 gene transcription.

In addition to the transcriptional regulation, a recent study from our group also showed that HO-1 is subjected to post-translational regulation by the ubiquitin-proteasome system through an ER-associated degradation pathway. Proteasome inhibition significantly decreases HO-1 protein degradation. Increased HO-1 expression by MG-132, a proteasome inhibitor, has been shown to protect astrocytes from heme-mediated oxidative injury. Whether the ubiquitin-proteasome-mediated HO-1 protein turnover is altered in various cellular circumstances is currently unclear. Delineating the detailed mechanisms regulating HO-1 ubiquitination thus is necessary for a further understanding of the physiological significance of HO-1 turnover.

**HO-1 in vascular system**

Numerous studies have supported the multi-functional roles of HO-1 in the vascular system, including vascular tone regulation, anti-smooth muscle proliferation, anti-endothelial apoptosis, and angiogenesis. The effects of HO-1 appear to be mediated in large part by the actions of its reaction byproducts, CO and bilirubin. In the vascular system, nitric oxide (NO) released from endothelial cells in response to shear stress and activation by various factors is well established as a major signaling molecule that activates soluble guanylate cyclase (sGC), which in turn increases intracellular cGMP and leads to vasodilatation, inhibition of smooth muscle cell proliferation, anti-thrombogenic effects, and anti-inflammatory responses in vascular system. Compared to NO, which is a free radical with one unpaired electron, CO is a relatively stable gas. However, both gases share some similar functions. CO is also able to promote vasodilatation through activating soluble guanylate cyclase, although it has a lower efficacy than NO. CO produced from hypoxia-stimulated rat aortic smooth muscle cells can decrease the expression of endothelin-1 and platelet-derived growth factor-B in endothelial cells. Moreover, CO can affect K+ channel activity in smooth muscle and regulate its relaxation and contraction. CO has also been shown to inhibit vascular smooth muscle cell proliferation through a cGMP-dependent pathway. On the other hand, bilirubin can exert anti-proliferative effect on smooth muscle cells through its antioxidant property. In view of the profound effects of CO and bilirubin on vascular cells, it is envisaged that HO-1 has a significant impact on the development of atherosclerosis, which represents a chronic pathological process associated with multiple oxidative stress of the vasculature. Studies from several laboratories, including our group, have demonstrated that HO-1 exerts potent anti-atherogenic effects via multiple pathways. HO-1 overexpression in vasculature reduces iron deposition in atherosclerotic lesions. Moreover, the inhibitory effects of CO and bilirubin on monocyte transmigration through endothelium, smooth muscle cell proliferation and inflammatory gene expression appear to contribute to various degrees to the protective effect of HO-1 in atherosclerosis. Likewise, HO-1 overexpression in arterial walls reduces neointima formation subsequent to vascular injury through the anti-proliferative effect of CO and bilirubin and the anti-thrombotic and anti-inflammatory effects of CO.

The first link between HO-1 and angiogenesis was demonstrated in a study showing that overexpression of HO-1 in endothelial cells enhanced cell proliferation. The increased proliferation is associated with cell cycle progression with a reduction in p21 and p27 in the endothelial cells. HO-1 has also been shown to induce VEGF synthesis and function. Inhibition of HO-1 activity by tin protoporphyrin prevents VEGF synthesis induced by hypoxia in smooth muscle. Conversely, VEGF induces HO-1 expression. Inhibition of HO-1 activity by tin pro-
toporphyrin abolishes VEGF-induced endothelial cells proliferation and tube formation, indicating the close interaction between VEGF and HO-1.\(^{(43)}\) Tumor infiltrating macrophages have been found to enhance HO-1 expression and accentuated angiogenesis in human gliomas and melanoma.\(^{(44,45)}\) Nevertheless, inflammation-induced angiogenesis can be attenuated by increasing HO-1 activity in macrophages,\(^{(43)}\) which suggests that HO-1 has a dual effect on angiogenesis. It is well documented that under hypoxia conditions the transcriptional factor HIF-1\(\alpha\) is highly induced and mediates the expression of many hypoxia-responsive genes, including VEGF. The hypoxia response element is present in the HO-1 gene promoter. HO-1 expression has been shown to be induced by hypoxia in vascular cells via HIF-1-mediated gene transcription.\(^{(46)}\) It is conceivable that the interplays between HO-1 and VEGF induced by hypoxia might augment the angiogenic response in ischemic tissues.

In addition to VEGF, stromal cell-derived factor-1 (SDF-1) has also been shown to play an important role in the new vessel formation in adult tissues. SDF-1 is a chemokine and reacts with a single high-affinity receptor, CXCR4. SDF-1 controls the trafficking of the primitive CXCR4\(^+\)-hematopoietic cells into and away from the bone marrow. Moreover, it promotes the migration of bone marrow-derived CXCR4\(^+\)-endothelial progenitor cells as well as hematopoietic cells to local tissues, where they participate in neovascularization.\(^{(47)}\) SDF-1 knockout mice are embryonically lethal because of abnormal vascular development.\(^{(48)}\) SDF-1 increases HO-1 expression, which in turn mediates SDF-1-induced angiogenic response of endothelial cells.\(^{(49)}\) HO-1 deficiency in endothelial cells causes defective angiogenesis upon SDF-1 stimulation. Our group recently showed that forced expression of HO-1 in the ischemic heart via adeno-associated virus-mediated gene transduction can induce VEGF and SDF-1 concurrently, which results in the recruitment of bone marrow-derived c-kit\(^+\)-stem cells to the infarcted myocardium and increases myocardial angiogenesis.\(^{(50)}\) Concomitant administration of both VEGF and SDF-1 neutralizing antibodies significantly attenuated HO-1-mediated neovascularization and protection during myocardial infarction, highlighting the cooperative roles of both factors in HO-1 mediated angiogenesis and protection.\(^{(50)}\) The impact of HO-1 on SDF-1 expression and bone marrow-derived stem cell mobilization has also been observed in a hind-limb ischemia model by others.\(^{(53)}\) In line with these findings, more recently, our group also reported that an increase in systemic HO-1 expression enhanced reendothelialization after vascular injury through promoting the mobilization of endothelial progenitor cells from bone marrow.\(^{(52)}\)

**HO-1 in the heart**

HO-1 overexpression protects the myocardium from ischemic and reperfusion injury.\(^{(53)}\) Several lines of evidence suggest that the anti-inflammatory properties of CO and the anti-oxidant effects of bilirubin mediate the myocardial protection induced by HO-1. In a rat model, CO or biliverdin alone did not alter the survival of heart grafts, while a combined therapy was able to increase the survival from 0% to 80%.\(^{(54)}\) An earlier study from our group demonstrated that HO-1 has a role in the myocardial remodeling response.\(^{(55)}\) Cardiac hypertrophy induced by angiotensin II can be significantly suppressed by HO-1 overexpression either by cobalt protoporphyrin or HO-1 adenovirus. Our results support the hypothesis that bilirubin suppresses angiotensin II-induced cardiac hypertrophy via a reduction in reactive oxygen species production. Others have also shown that antioxidants are effective at preventing cardiomyocyte hypertrophy and HO-1 induction attenuates cardiac hypertrophy in stroke-prone SHR rats.\(^{(56)}\) Reactive oxygen species are implicated in various pathological myocardial dysfunction and, therefore, the attenuation of reactive oxygen species by HO-1 is considered to be a potential therapeutic target in myocardial diseases.

**HO-1 in macrophages**

Our group has found that HO-1 expression is prominent in the endothelium and macrophages of human and mouse atherosclerotic vessels.\(^{(55)}\) HO-1 expression is induced in macrophages after treatment with oxidized low density lipoprotein.\(^{(55)}\) Another group has also shown that HO-1 is critically involved in macrophage activation toward the M2 phenotype,\(^{(58)}\) which is an anti-inflammatory phenotype. Moreover, a study has shown that HO-1 null macrophages exhibit increased levels of reactive oxygen species, have higher proinflammatory cytokines and undergo greater foam cell formation.
partly due to the increase in scavenger receptor A expression.\(^{59}\) Further evidence also supports the multiple functions of HO-1 in macrophages. Upon lipopolysaccharide stimulation, HO-1 is recruited to the caveolae by a p38 MAPK-dependent mechanism and this inhibits proinflammatory signaling.\(^{60}\) This effect is through suppression of the interaction of caveolin-1 with toll-like receptor 4, which is the principle membrane receptor for lipopolysaccharide. We have shown that the potent anti-inflammatory cytokine interleukin-10 (IL-10) induces expression of HO-1 in a p38 MAPK-dependent mechanism in macrophages.\(^{61}\) IL-10-mediated protection against LPS-induced septic shock in mice is significantly attenuated by an inhibitor of HO-1, illustrating the important role of HO-1 as a downstream effector of IL-10. As HO-1 has diverse effects that affect inflammation, apoptosis, hypoxia and angiogenesis, it is not surprising to find that HO-1 has clinical relevance in various cardiovascular diseases.

**Clinical perspectives of HO-1 in cardiovascular diseases**

**Coronary artery disease**

The direct evidence of the clinical significance of HO-1 in coronary artery disease comes from a study demonstrating that HO-1 expression and activity are associated with atherosclerosis. Human arterial samples were obtained from normal subjects during surgery for vascular trauma or from patients with atherosclerotic diseases. Interestingly, VEGF protein and HO-1 activity, as measured by bilirubin release per mg of aorta, were only present in the advanced atherosclerotic lesions.\(^{62}\) Furthermore, leukocytes from patients with coronary artery diseases also express HO-1 and the level of HO-1 expression was correlated with the severity of their disease, with patients suffering from acute myocardial infarction being highest, followed by patients with unstable angina.\(^{63}\) It has also be shown that among patients with documented coronary artery disease, HO-1 level is correlated with plaque burdens.\(^{64}\)

In terms of genetic studies the GT dinucleotide repeats in the promoter region of the human HO-1 gene have been shown to modulate HO-1 gene transcription.\(^{65,66}\) The number of the (GT)\(_n\) repeat is highly polymorphic and studies from our group and others have demonstrated that promoters containing longer (GT)\(_n\) repeats show lower transcriptional activity. Microsatellite polymorphisms have been reported to be associated with coronary restenosis after balloon angioplasty, or stents implantation, abdominal aortic aneurysm, and renal allografting.\(^{67}\) Shorter GT repeat in HO-1 gene promoter have been associated with a lower inflammatory response and reduced restenosis after balloon angioplasty. In addition, diabetic patients with longer (GT)\(_n\) repeats show increased susceptibility to the coronary artery diseases. Finally, a single nucleotide polymorphism, T(-143)A, has been identified and the AA/TA+TT variant was found to be associated with increased hypertension in women.

**Cerebrovascular disease**

HO-1 is expressed in the human brain and is associated with brain tumors and neurodegenerative diseases. Following traumatic brain injury, an accumulation of HO-1-positive microglia or macrophages at the hemorrhagic lesion has been noted to be present from 6 hours to 6 months.\(^{68}\) However, during cerebral infarction, macroglia or macrophages with HO-1 expression have been noted only within focal hemorrhages.\(^{68}\) It is not known if these HO-1-positive cells are a response to the local hemorrhage or whether they are able to exert a protective role during brain injury after trauma or stroke. The clinical relevance of HO-1 in cerebrovascular events is controversial. In patients with advanced peripheral artery diseases, HO-1 promoter microsatellite polymorphism do not seem to be correlated with the cerebrovascular event, unlike coronary events.\(^{69}\) A follow-up study of 472 patients with advanced peripheral artery diseases for 21 months has shown that persons with short (GT)\(_n\) repeats have a lower hazard ratio for coronary events;\(^{70}\) however, no significant difference was found for cerebrovascular events and mortality.\(^{71}\) Nonetheless, in cerebral aneurysms, the HO-1 promoter polymorphism was shown to correlate with an increased risk.\(^{71}\)

**HO-1 and therapeutic agents**

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are therapeutic agents for the treatment of hypercholesterolemia. The Scandinavian Simvastatin Survival Study (4S), the West of Scotland Coronary Prevention Study (WOSCOPS), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/
TexCAPS) and the Heart Protection Study (HPS), have demonstrated the effects of statins in the primary and secondary prevention of cardiovascular disease. Statins also have cholesterol-independent or pleiotropic effects.\(^{(72)}\) By inhibiting the conversion of HMG-CoA to R-mevalonic acid, statins prevent the synthesis of isoprenoids, which are the precursors of cholesterol biosynthesis. These intermediates serve as important lipid attachments for the post-translational modification of proteins, such as Ras, Rho and Rac. Given that these isoprenylated proteins control diverse cellular functions, recent studies have suggested that statins may have immunomodulation, anti-inflammatory and anti-senescent effects.\(^{(73-75)}\)

Simvastatin has been shown to induce HO-1 in human smooth muscle cells.\(^{(76)}\) This effect was noted only in smooth muscle cells but not in endothelial cells or macrophages. Blocking HO-1 activity by zinc protoporphyrin or a small interfering RNA decreased the anti-inflammatory effect of simvastatin through inhibition of nitric oxide production, NF-\(\kappa\)B activation and p21. The Akt and p38 MAPK pathways appeared to mediate the effect of simvastatin on HO-1 induction. This finding suggests that statins may provide a new therapeutic possibility for the activation of HO-1. Moreover, fenofibrate, rosiglitazone and troglitazone, which are ligands of the peroxisome proliferators-activated receptors (PPAR), have been shown to increase the expression of HO-1.\(^{(77)}\) These PPAR ligands have been shown to potently inhibit the development of atherosclerosis and coronary restenosis after stent implantation. Evidence has suggested that these effects are not only due to insulin sensitization but also are related to their anti-inflammatory effects.\(^{(78)}\) It has been shown that two PPAR responsive elements are present in the HO-1 promoter and both PPAR\(\alpha\) and PPAR\(\gamma\) can directly regulate HO-1 gene transcription.\(^{(77)}\) The HO-1 promoter polymorphism critically affects transcriptional activation activity by PPAR\(\alpha\) or PPAR\(\gamma\). Interestingly, aspirin also increases HO-1 protein level in a dose-dependent fashion in human umbilical endothelial cells.\(^{(79)}\) The nitric oxide synthase blocker L-NAME is able to inhibit HO-1 induction by aspirin, suggesting a NO-dependent pathway. Other pharmacological agents, such as curcumin, resveratrol, cyclosporine, rapamycin and probucol, have also been shown to induce HO-1.\(^{(27)}\)

Nevertheless, the clinical applications of these agents to augment HO-1 expression in the various disease states remain to be established.

**Conclusion**

As summarized in Table 1, HO-1 exerts multifunctional roles in the cardiovascular system and modulates the development of various diseases. HO-1 cooperates with its downstream products, CO and bilirubin to exert diverse cellular protection effects and provide potential disease therapeutic targets. However, there are still gaps between the basic findings and their clinical application. Currently, there is no large-scale clinical study providing solid evidence to prove the usefulness of HO-1 therapeutics in patients, partly because of lacking specific HO-1

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<th>Disease setting</th>
<th>Effect</th>
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<tr>
<td>Atherosclerosis</td>
<td>Smooth muscle cell proliferation</td>
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<td>Inflammatory response</td>
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<td></td>
<td>Iron deposition</td>
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<td>Smooth muscle cell proliferation</td>
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<td>Inflammatory response</td>
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<td>Thrombosis</td>
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<td>Limb ischemia</td>
<td>Neovascularization</td>
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activators. As both CO and bilirubin also play important roles in cardiovascular protection, the potential of these chemicals as clinical therapeutics versus HO-1 are still unclear and needed to be dissected further. A serum or plasma marker for HO-1 will be important and useful addition in the future because it would help with the clinical assessment of the role of HO-1 in cardiovascular diseases. At present, there is no specific and sensitive marker for HO-1 activity in vivo. Clinical studies have primarily focused on the genetic association of HO-1 and various diseases. It will be important to delineate the pathophysiological responses and activity of HO-1 in patients with cardiovascular diseases of various severities, as HO-1 is an inducible enzyme and its activity or function may vary greatly in patients with different disease status.

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第一型血基質氧化酶與心血管疾病：
分子作用機制與臨床之重要性

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血基質氧化酶 (Heme oxygenase) 是血基質代謝過程中的速率限制酶，可將血基質代謝為鐵、膽紅素、膽紅素以及一氧化碳。目前已知血基質氧化酶有二種異構酶，分別為誘發型第一型血基質氧化酶及持續表現型第二型血基質氧化。和第二型血基質氧化酶不同的是，第一型血基質氧化酶會被很多不同的誘發因子所誘發出來，如發炎、局部缺血、缺氧、重金屬、
一氧化氮及氧化劑。雖然第一型血基質氧化酶在血基質及紅血球代謝有很大的功能，在很多不同的細胞功能中也扮演重要的角色，例如抗氧化作用、抗發炎作用、血管新生、細胞凋亡及動脈硬化。第一型血基質氧化酶的產物一氧化碳及膽紅素也有重要的細胞訊息傳導作用 並且影響很多細胞功能。目前已有許多研究證據顯示第一型血基質氧化酶在臨床疾病上的重要性，如動脈硬化、肉狀動脈疾病，心臟肥厚、糖尿病及癌症，第一型血基質氧化酶都扮演著重要的生理病理調整角色。(長庚醫誌 2010;33:13-24)

關鍵詞：第一型血基質氧化酶，一氧化碳，膽紅素，心血管疾病