

Association between HO-1 gene promoter polymorphisms and diseases (Review)

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Abstract. Heme oxygenase-1 (HO-1) is an inducible cyto-protective enzyme that degrades heme into free iron, carbon monoxide and biliverdin, which is then rapidly converted into bilirubin. These degradation products serve an important role in the regulation of inflammation, oxidative stress and apoptosis. While the expression level of HO-1 is typically low in most cells, it may be highly expressed when induced by a variety of stimulating factors, a process that contributes to the regulation of cell homeostasis. In the 5'-non-coding region of the HO-1 gene, there are two polymorphic sites, namely the (GT)_n dinucleotide and T(-413)A single nucleotide polymorphism sites, which regulate the transcriptional activity of HO-1. These polymorphisms have been shown to be closely associated with the occurrence and progression of numerous diseases, including cardiovascular, pulmonary, liver and kidney, various types of cancer and viral diseases. The present article reviews the progress that has been made in research on the association between the two types of polymorphisms and these diseases, which is expected to provide novel strategies for the diagnosis, treatment and prognosis of various diseases.

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1. Introduction

Heme oxygenase-1 (HO-1), also known as heat shock protein 32, is the rate-limiting enzyme in the heme degradation pathway that degrades hemoglobin into biliverdin, free iron and carbon monoxide (CO) (1). Biliverdin is subsequently reduced to bilirubin via biliverdin reductase. Both biliverdin and bilirubin are bile pigments with antioxidant properties (2). Endogenous CO can act as a second messenger, thereby affecting a variety of physiological and pathological processes, including cell proliferation, inflammation, apoptosis and injury (3). As a cytoprotective enzyme, HO-1 serves an important role in maintaining cell homeostasis.

To date, three HO polymorphic isoenzymes have been identified, namely HO-1, HO-2 and HO-3, of which HO-1 is inducible. The HO-1-encoding gene is located on the long arm of chromosome 22q12 in the human body, with a total length of 6.8 kb (4). HO-1 is expressed in a variety of tissues, including the liver, spleen, kidney, heart, lung, brain, blood vessels, smooth muscle cells and endothelial cells, among which the highest expression is observed in the liver, spleen and kidney (5,6). Under normal physiological conditions, the expression of HO-1 is relatively low in most tissues. However, under various pathophysiological stress or stimulation conditions, such as hypoxia, ultraviolet light, inflammatory mediators, heme, ischemia and other harmful stimuli, HO-1 expression is induced to protect cells against oxidative and inflammatory damage (7,8). In the presence of the aforementioned stimulatory factors, the induced expression of HO-1 is primarily affected by redox-sensitive transcription factors, including nuclear factor erythroid 2-related factor 2 (Nrf2), activator protein 1 (AP1), hypoxia-inducible factor (HIF) and BTB and CNC homology 1 (Bach1) (9). In addition, a

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Abbreviations: HO-1, heme oxygenase-1; CO, carbon monoxide; CHD, coronary heart disease; S, short; L, long; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury

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large number of epidemiological genetic studies have shown that the expression of HO-1 is regulated by genetic polymorphisms in the promoter of its gene, which might be associated with a variety of diseases, such as coronary atherosclerosis, rheumatoid arthritis and viral diseases (10-13).

The present review focuses on the clinical evidence that HO-1 gene polymorphisms are associated with the incidence and outcome of different diseases. To further understand this association, a brief discussion of the regulation of HO-1-induced expression mediated by transcription factors is included.

2. Regulation of HO-1 expression

As a stress-induced cytoprotective enzyme, the investigation of the molecular mechanism underlying HO-1 regulation began with studies on how various stress stimulation conditions, including stress, hypoxia and small-molecule inducers, could influence the activity of the enzyme. Under these stress conditions, the expression of HO-1 is primarily regulated by redox-sensitive transcription factors, including Nrf2, AP1, HIF and Bach1. The present review discusses the mechanisms through which each of these factors regulate HO-1.

Nrf2 is considered to be the primary transcription factor that regulates the expression of HO-1 (14). Under basic conditions, Nrf2 can form a protein complex with Kelch-like ECH-associated protein 1 (KEAP1) in the cytoplasm, which inhibits the activity of Nrf2 via proteasome-mediated degradation of Nrf2 (15,16). When cells are exposed to chemical or physical stimuli, Nrf2 separates from KEAP1 and transfers to the nucleus, where it binds to MAF bZIP transcription factor (Maf). The Nrf2/Maf heterodimers bind the antioxidant response element (ARE), leading to the transcriptional activation of antioxidant genes, including the HO-1 gene (17,18). Bach1, a heme sensor, acts as a major transcriptional repressor of HO-1 expression. Bach1 impairs the DNA-binding activity of Nrf2 by competing with Nrf2 for binding to the AREs of numerous antioxidant genes under basal conditions. High levels of heme in cells can cause Bach1 to dissociate from AREs, leading to nuclear export and subsequent proteasome-mediated degradation of Bach1. Under these circumstances, transcriptional expression of HO-1 occurs (19,20). In general, in response to various stress stimuli, the feedback loop formed by Nrf2, KEAP1 and Bach1 has a pivotal role in regulating the expression of HO-1.

Other transcriptional factors have been shown to be involved in the regulation of HO-1 expression, including HIF-1, AP1 and NF- κ B (21,22). Similarly to Nrf2, these factors can combine with the *cis*-regulatory element of the HO-1 gene, resulting in an increase in HO-1 expression (21). HIF-1, a redox-responsive transcription factor, induces HO-1 expression in different cell types under hypoxic conditions (23-26). However, a specific mutant of HIF-1 lost its DNA-binding activity, which resulted in inhibition of HO-1 expression (27). Mechanistic studies have shown that HIF-1 α /HIF-1 β heterodimers are necessary for hypoxia-induced HO-1 expression, since hypoxia induces the expression of HIF-1 α , which binds to specific DNA sequences dependent on HIF-1 β (27). AP1 transcriptional factor is generated by dimers of the Jun and Fos family proteins. AP1 is able to bind to tetradecanoylphorbol-13-acetate-responsive elements

of the HO-1 gene promoter (28,29), subsequently leading to the upregulation of HO-1 expression, which has been demonstrated by functional studies and sequence analysis of the promoter (21,30-32). Similarly to AP1, the NF- κ B family of transcription factors are dimerization complex factors formed by REL proto-oncogene, NF- κ B subunit family proteins. NF- κ B homodimers comprising p52 and p50 are transcription repressors, whereas NF- κ B heterodimers formed by p65 and p50 act primarily as transcription activators (21,33). AP1 and NF- κ B have been shown to regulate HO-1 expression primarily in immune cells, thereby fulfilling an important role in protecting against inflammation-mediated damage, including that mediated by reactive oxygen species (34).

In addition to the direct regulation mediated by a range of transcription activators, a large number of HO-1 inducers are also able to indirectly activate the expression of the protein through acting on the protein kinase signaling pathway. Numerous plant-derived polyphenols have been found to induce HO-1 gene expression by activating the MAPK, PI3K/AKT and AMP-activated protein kinase (AMPK) signaling pathways (35-37). For example, salvianolic acid A, a plant-derived polyphenol that has been widely studied, provides significant protection in several cell types following exposure to different stimuli by activating the PI3K/Akt/mTOR complex 1 or MAPK ERK/p38 signaling pathways (38-40). Quercetin, another polyphenol antioxidant, activates the MAPK signaling pathway, thereby inducing the expression of HO-1, which provides protection against apoptosis and inflammation (41,42). Additionally, plant-derived polyphenols have been reported to show antioxidative stress and anti-inflammatory properties via AMPK-dependent induction of HO-1 (43,44). The precise mechanism by which the protein kinase signaling pathway induces the expression of HO-1 involves the cross-talk of transcription factors, including Nrf2, AP1 and HIF-1, and has been previously reviewed in detail (21,34). In general, the induced expression of HO-1 is an adaptive strategy that enables cells to achieve self-protection under stress conditions. However, a variety of genetic epidemiological studies have shown that there are two important genetic polymorphisms in the promoter region of the HO-1 gene (45-47). These polymorphisms determine the expression level of HO-1 and affect several diseases, such as cardiovascular, pulmonary, liver, renal, cancer and viral diseases.

3. HO-1 promoter polymorphism

HO-1 gene polymorphisms are primarily based on two sites: The (GT) n double nucleotide polymorphism (also called microsatellite polymorphism) and the T(-413)A single nucleotide polymorphism (SNP), both of which can regulate HO-1 gene transcription under specific conditions (45). These two polymorphic sites on the HO-1 gene promoter are shown in Fig. 1.

(GT) n double nucleotide polymorphism. Of the two polymorphism sites found in the HO-1 promoter region, the (GT) n dinucleotide repeat polymorphism (rs3074372) occurs more commonly. The number of (GT) n repeats ranges from 12-45 repeats (48), and the distribution of (GT) n repeats is bimodal, with alleles of \sim 23 and 30 repeat lengths (5,12,48-52).

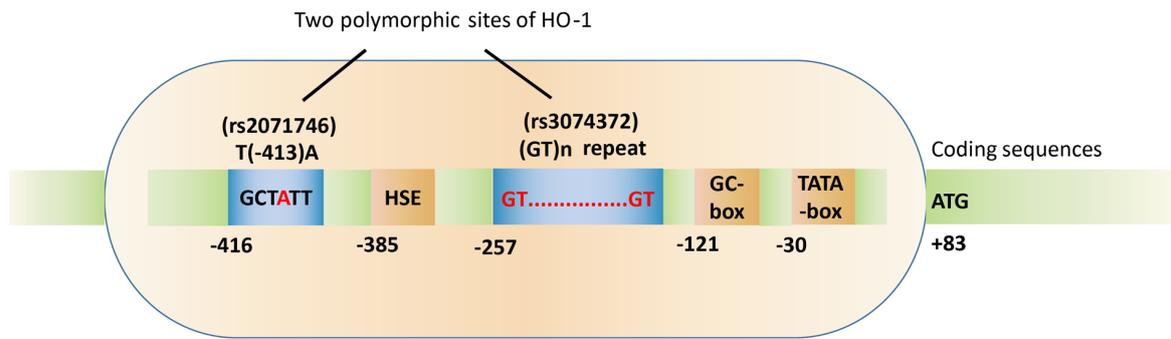


Figure 1. Polymorphic sites on HO-1 gene promoter. The two polymorphic sites including the (GT)_n dinucleotide repeat polymorphism (rs3074372) and the T(-413)A single nucleotide polymorphism (rs2071746) in the 5'-flanking region of the heme oxygenase-1. The number of (GT)_n repeats ranges from 12-45. HO-1, heme oxygenase-1; HSE, heat shock element.

According to this genetic distribution in humans and the effect of GT_n repeats on the transcriptional activity of HO-1, short (S) alleles have been defined as having <25 GT_n repeats, whereas those with ≥25 repeats were defined as long (L) alleles (49,53). Alternatively, other studies have used a different classification method: S alleles have been denoted by <27 GT, middle alleles (M) as 27-32 GT and L alleles as ≥33 GT (11,54). The biological function generated through the use of either classification system should be consistent, taking into account the (GT)_n distribution frequency (5).

Through the use of the luciferase reporter gene system *in vitro*, previous studies have confirmed that S alleles are associated with a higher transcriptional activity of HO-1 compared with L alleles (51,52). Consistent with this, genetic epidemiological studies have shown that subjects with S alleles have higher levels of HO-1 mRNA compared with subjects with L alleles (12,13). Moreover, when lymphocytes isolated from humans were exposed to H₂O₂ stimulation *in vitro*, the HO-1 expression level in cells with S alleles was found to be higher compared with that of cells with L alleles. Functionally, lymphocytes with S alleles exhibit a stronger antiapoptotic ability (11). On the other hand, L (GT)_n repeats have been demonstrated to be associated with a higher susceptibility to the development of numerous diseases, such as hypertension, atherosclerosis, acute kidney injury, breast cancer and pancreatitis. Clinical studies have shown that the (GT)_n repeat length of the HO-1 promoter is correlated with the progression of a variety of diseases, such as hypertension, atherosclerosis, and acute kidney injury (55-57).

T(-413)A SNP. T(-413)A SNP (rs2071746), another HO-1 promoter polymorphism, was detected by reverse transcription-quantitative PCR. Yamada *et al* (52) transfected plasmids containing different HO-1 gene promoters into bovine aortic endothelial cells to detect functional differences caused by SNPs. The results obtained showed that cells containing the A(-413)-(GT)₃₀ allele were able to significantly enhance the biological activity of HO-1. Several studies have subsequently confirmed that the A allele is also associated with a high transcription level of HO-1, which correlates closely with the occurrence and progression of certain human diseases, including cardiovascular, and liver diseases (58-60). A previous study reported that the AA genotype of T(-413)A could significantly reduce the occurrence of myocardial

infarction and angina pectoris (61). In addition, the survival rate of transplanted livers was shown to be significantly higher following liver transplantation from donors who carried the A allele (62).

Population characteristics of HO-1 gene promoter polymorphisms. According to a study of HO-1 gene promoter polymorphism in Caucasian and East Asian populations, the distribution of (GT)_n alleles showed a bimodal pattern with (GT)₂₃ and (GT)₃₀ being the two most common alleles in the two groups (50,51). However, the distribution of (GT)_n alleles showed a trimodal pattern with peaks at (GT)₂₃, (GT)₃₀ and (GT)₃₉ in African-American populations (50). Compared with Caucasian populations, meta-analysis showed that East Asian populations had more S alleles and fewer L alleles (58). (GT)_n polymorphism includes three genotypes, namely SS, SL and LL. East Asian populations showed higher SS frequencies, ranging from 15 to 25%, whereas Caucasian populations displayed SS frequencies ranging from 6 to 17% (58). The SS genotype was associated with a lower incidence of chronic diseases, such as coronary heart disease and rheumatoid arthritis (12,58). The incidence of rheumatoid arthritis in East Asian populations is lower than that in Caucasian populations, which might be related to the higher SS genotype in East Asians. In addition, a recent study showed that Caucasian American populations have a higher SS allele frequency compared with African American populations, which might be the cause of higher neurocognitive impairment caused by human immunodeficiency virus (HIV) infection in African American populations (50). Similarly, the T(-413)A SNP polymorphism genotype also contains three genotypes, namely AA, AT and TT. These genotypes also differs between Caucasian and East Asian populations. Meta-analysis showed that East Asian populations had a lower AA genotype (~22%) compared with Caucasian populations (~35%). People with the AA genotype displayed a lower risk of coronary heart disease (58).

Mechanism of promoter polymorphisms regulating HO-1 expression. To date, the mechanism through which the T(-413)A and (GT)_n gene polymorphisms regulate the expression of HO-1 has not been elucidated. A potential explanation may be that (GT)_n microsatellite repeats tend to form a Z-DNA conformation, such as a left-handed double-helix structure (63). The Z-DNA conformation only occurs rarely in the

genome, although its incidence does increase under certain conditions, such as the presence of a purine/pyrimidine-alternating sequence, DNA supercoiling and a high concentration of salt and certain cations (5,64). During the transcription process, the local Z-DNA conformation reduces the transcription activity of DNA. Therefore, the L (GT)_n microsatellite repeats in the promoter tend to form a Z-DNA conformation, which consequently reduces the transcriptional activity of HO-1. In addition, a previous study showed that the T(-413)A and (GT)_n polymorphisms may be involved in the splicing and translation of the HO-1 transcript (65). An extra exon (Exon1a) was identified for the first time in the 5'-untranslated region (5'-UTR) of HO-1. Moreover, the T(-413)A and (GT)_n loci are located between Exon1a and Exon1. T(-413)A and (GT)_n are located in the primary transcripts of HO-1 as alternative intronic or exonic elements. Rapid amplification of cDNA ends and luciferase reporter assays were subsequently used to confirm that T(-413)A and (GT)_n are involved in 5'-UTR alternative splicing of the HO-1 primary transcript, which may result in translational control of HO-1 through regulating mRNA stability and translational efficiency (65). Moreover, expression of Exon 1a induced by hemin in hepatoma HepG2 cells is shown to decrease mature HO-1 mRNA isoform translation, which might explain the previous finding that human HO-1 mRNA and protein levels fail to correlate (66).

4. Association between HO-1 gene polymorphism and clinical diseases

As a cytoprotective enzyme, the intracellular expression level of HO-1 is influenced by the (GT)_n dinucleotide polymorphism and T(-413)A SNP in its promoter region. Several studies have shown that these two polymorphisms affect the occurrence and progression of a variety of diseases, including liver and kidney, lung, cardiovascular, cancer and viral diseases (48,52,55-58,67). The association between two HO-1 promoter polymorphisms and diseases are summarized in Table I.

Cardiovascular disease. HO-1 is a protective factor for cardiovascular diseases (68). Previous studies have shown that the level of serum bilirubin, a downstream product of HO-1, is negatively correlated with the occurrence of coronary heart disease (CHD), and lower levels of serum bilirubin increase the risk of CHD. Through a correlation analysis, Zhang *et al* (58) demonstrated that the HO-1 (GT)_n repeat length polymorphism and T(-413)A SNP were both associated with a risk of CHD following percutaneous coronary intervention. Patients with the S allele of HO-1 (GT)_n had a reduced risk of restenosis compared with those with the L allele of HO-1 (GT)_n. Similarly, the HO-1 A allele of T(-413)A was associated with a reduced risk of CHD. Consistent with the aforementioned results, Liang *et al* (69) showed that the HO-1 promoter (GT)_n repeat sequence in patients with CHD with a reduced ejection fraction was longer compared with that in patients with CHD with moderate ejection fraction.

Ono *et al* (59) demonstrated that the HO-1 AA genotype is associated with an increased incidence of hypertension in a female population. Wenzel *et al* (55) reported that the individuals carrying the HO-1 L allele had an increased risk

for the prevalence of arterial hypertension and higher overall mortality. In line with this, another study demonstrated that the HO-1 S allele may serve a protective role against environmental stressors in blood pressure regulation and cardiovascular mortality risk in hypertensive individuals (70). Therefore, the (GT)_n repeat or SNP polymorphisms may be used as molecular markers for screening individuals who are at risk of hypertension.

Atherosclerosis is an inflammatory disease (71). As an anti-inflammatory protein, HO-1 has been confirmed to have a protective effect on blood vessels and is able to inhibit the formation of atherosclerotic lesions (72-74) and thrombosis (75). Liang *et al* (76) also found that the HO-1 promoter (GT)_n repeat sequence was longer in patients with microvascular angina compared with that in healthy controls. Similarly, Pechlaner *et al* (56) demonstrated that there is a strong correlation between the HO-1(GT)_n repeat polymorphism and cardiovascular disease risk in subjects for whom the number of (GT)_n repeats was ≥ 32 . Taken together, these studies provided some indicators for how atherosclerosis may be accelerated and antioxidant defenses decreased in high-risk vascular groups.

In conclusion, individuals carrying the L allele of HO-1 (GT)_n were shown to have an increased risk of CHD, hypertension and atherosclerosis, whereas the A allele of T(-413)A in the HO-1 gene promoter is associated with a lower risk of CHD, but an increased risk of hypertension. However, these controversial conclusions might have resulted from the limited number of subjects and different populations included in the CHD studies, thus these limitations also need to be taken into consideration.

Pulmonary disease. The induction of HO-1 expression is considered to be an important protective mechanism involved in acute and chronic lung diseases, and HO-1 is an important enzyme that exerts antioxidant protective effects in the lung (77). HO-1 gene polymorphism is closely associated with chronic obstructive pulmonary disease (COPD) (52,78,79).

A previous study confirmed that insufficient or inhibited levels of HO-1 expression are an important internal factor for inducing the occurrence of COPD (80). Zhang *et al* (81) found that HO-1 exerts a protective function on the lungs, and the number of GT repeats was shown to influence the effects of oral N-acetylcysteine treatment. Patients with L (GT)_n alleles were shown to have a much higher rate of deterioration compared with patients that lacked the L alleles. From this study, it may be concluded that HO-1 gene polymorphism has an important role in COPD. Yamada *et al* (52), Du *et al* (78) and Zhou *et al* (79) also demonstrated that the L (GT)_n allele frequency in patients with COPD was significantly higher compared with that in the control group.

Liver disease. HO-1 has also been shown to protect allografts against ischemia/reperfusion and immune rejection. By studying 60 patients with allogeneic orthotopic liver transplantation and their accompanying donors, Zhang *et al* (82) found that donor-derived HO-1 gene promoter polymorphism exerted a protective effect on allograft function following orthotopic transplantation. A short (GT)_n sequence ($n < 25$ repeats) leads to increased HO-1 transcriptional activity, and a series of

Table I. Association between two HO-1 promoter polymorphisms and a variety of diseases.

A, (GT)n dinucleotide polymorphism			
Disease	Polymorphism	P-value	(Refs.)
Cardiovascular disease			
Coronary heart disease	S (GT)n repeats reduce the risk of coronary heart disease or restenosis	P<0.05	(58,68)
Hypertension	Carriers with the L (GT)n allele have an increased risk of hypertension, whereas the S (GT)n allele may play a protective role	P<0.05	(55,70)
Atherosclerosis	Subjects with (GT)n repeats ≥ 32 display an increased risk of cardiovascular disease and enhanced atherosclerosis progression	P<0.01	(56)
Pulmonary disease			
Chronic obstructive pulmonary disease	L (GT)n allele is a high risk factor for chronic obstructive pulmonary disease	P<0.01	(52,78,79)
Liver disease			
Liver transplantation	S (GT)n sequence (n<25) is beneficial to the functional improvement and survival of allografts	P<0.05	(82)
Renal disease			
Acute kidney injury	Carrying the L (GT)n allele increases the risk of acute kidney injury after heart surgery, whereas carrying S (GT)n allele increases the risk of acute kidney injury in patients with sepsis	P<0.05	(57,87)
Cancer			
Pancreatic cancer, melanoma	The S (GT)n allele sequence is associated with an increased risk and lesion of pancreatic cancer and melanoma	P<0.001 (pancreatic cancer) or P<0.05 (melanoma)	(88,89)
Acute lymphoblastic leukemia	Patients with S (GT)n repeats display chemotherapy resistance and chemo-induced neutropenia	P<0.05	(92)
Breast cancer, esophageal squamous cell carcinoma and laryngeal squamous cell carcinoma	L (GT)n repeats are associated with a higher risk of these type of cancer	P<0.05	(67,93-95)
Gastric cancer and lung adenocarcinoma	The effect of HO-1 promoter polymorphism on cancer may depend on a variety of factors, including tumor type, subject ethnicity and other factors	N/A	(96-98)
Viral disease			
HIV	S (GT)n allele inhibits neuroimmune activation, HIV-associated neuroinflammation and neurocognitive deficits	P<0.05	(10,48,50)
HCV	S (GT)n allele decreases the infection titer of HCV	P>0.05	(101)
Other disease			
Neonatal hyperbilirubin	S (GT)n repeat gene promoter results in a higher risk of neonatal hyperbilirubinemia	P<0.05	(103)
Rheumatoid arthritis	S (GT)n allele reduces the risk of rheumatoid arthritis and prevents the development of joint injury	P<0.05	(12,104)
Pancreatitis	HO-1 containing LL allele doubles the risk of pancreatic necrosis in patients with acute pancreatitis	P<0.05	(105)

Table I. Continued.

B, T(-413)A single nucleotide polymorphism			
Disease	Polymorphism	P-value	(Refs.)
Cardiovascular disease			
Coronary heart disease	The A allele reduces the risk of coronary heart disease	P<0.05	(58)
Hypertension	AA genotype increases the incidence of hypertension in a female population	P<0.01	(59)
Liver disease			
Liver transplantation	Patients carrying the T allele are more likely to develop esophageal varices compared with those carrying the A allele	P<0.001	(60)
Other disease			
Type II diabetes	Patients with the TT genotype are more prone to developing proteinuria	P<0.05	(106)
Ischemic heart disease	The AA genotype of HO-1 reduces the incidence of ischemic heart disease	P<0.05	(61)

HO-1, heme oxygenase-1; L, long; S, short; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

transplantation models have demonstrated that HO-1 upregulation is beneficial to the functional improvement and survival of the allograft (82-85). In addition, studies have shown that patients with liver cirrhosis who carry the HO-1 T allele are more likely to develop esophageal varices than those with liver cirrhosis who carry the A allele. Therefore, the T allele of the HO-1 gene SNP is a risk factor for esophageal varices in patients with cirrhosis (60).

Renal disease. Acute kidney injury (AKI) refers to a multifactorial clinical syndrome caused by a variety of diseases, such as hypovolemia, diabetes, heart or lung disease (86). Leaf *et al* (57) demonstrated that repeated HO-1 polymorphism is associated with the development of AKI after cardiac surgery in adults, and carrying the HO-1 L (GT)_n sequence (n>27 repeats) increases the risk of AKI after cardiac surgery. Hemolysis may be the primary cause of AKI, but the factors associated with cardiac surgery are complex and varied. The most plausible mechanism that has been proposed to date is that the expression of HO-1 is reduced in patients with L (GT)_n repeats, resulting in a decrease in the decomposition of heme. Therefore, patients with reduced HO-1 expression caused by L (GT)_n repeats may have increased susceptibility to heme-related AKI during cardiac surgery.

In a different study, Vilander *et al* (87) classified the HO-1 (GT)_n repeat sequence in 300 patients with severe AKI sepsis and 353 patients without AKI sepsis. The alleles were classified according to the number of replicates. The short sequence S was defined as <27 repeats, the long sequence L was defined as ≥27 repeats and the very long sequence (L2) was defined as ≥34 repeats. Patients with at least one L2 sequence had lower plasma HO-1 concentrations compared with those without the L2 sequence. Patients with the S allele were found to be at an increased risk for AKI, and the adjusted odds ratio for each S allele was 1.3 in the additive genetic model. The conclusions of the aforementioned two studies are

different as the susceptibility factors of the study populations were different. In the study conducted by Leaf *et al*, patients underwent cardiopulmonary bypass surgery, whereas all patients were critically ill with sepsis in the study conducted by Vilander *et al*. In addition, urination criteria were not included in the study by Leaf *et al*, but patients with mild AKI were excluded in the study by Vilander *et al*. In conclusion, it is necessary to distinguish the different phenotypes of AKI clinical syndromes when conducting pathophysiological studies on patients with AKI.

Cancer. Increasing evidence on the association between HO-1 gene promoter polymorphism and cancer has been reported. Previous studies have shown that S (GT)_n repeats in the HO-1 promoter lead to higher transcriptional activity, which leads to an increased risk of pancreatic cancer and melanoma (88,89). In pancreatic cancer studies, patients with HO-1 S (GT)_n repeats developed cancer more rapidly and were more likely to experience recurrence. This finding was consistent with the fact that HO-1 expression in pancreatic tumors was higher compared with that in healthy tissues, and that HO-1 overexpression has been shown to accelerate the growth, angiogenesis and metastasis of pancreatic tumors (90,91). In pediatric patients with acute lymphoblastic leukemia, patients with HO-1 S (GT)_n repeats were associated with chemotherapy resistance and chemo-induced neutropenia (92). In other studies, L (GT)_n repeats in the promoter of the HO-1 gene have been reported to be associated with a higher risk of breast cancer, esophageal squamous cell carcinoma and laryngeal squamous cell carcinoma (67,93-95).

However, the effects of HO-1 promoter polymorphism in certain types of cancer have given rise to inconsistent results. For example, Lo *et al* (96) studied 183 patients with gastric cancer and 250 control patients in the Taiwan area. The results demonstrated that the L (GT)_n repeat of the HO-1 gene promoter was associated with a high frequency of gastric

cancer, and that the M (GT)_n repeat may have a protective effect on gastric adenocarcinoma with a low frequency of lymphatic vascular invasion. However, Sawa *et al* (97) found that, in the female Japanese population, HO-1 S (GT)_n repeats were associated with a risk of gastric cancer. This difference in the reported results may have been due to environmental factors and living habits. In addition, for lung adenocarcinoma, male smokers with the L allele had a significantly increased risk of lung adenocarcinoma compared with those with the non-L allele. In female non-smokers, L allele carriers did not differ between patients and controls (98). For sporadic colorectal cancer, studies have shown no association between HO-1 promoter (GT)_n repeat polymorphism/T(-413)A SNP and the risk of disease (99). Taken together, these findings suggested that the effect of HO-1 gene promoter polymorphism on cancer may depend on a variety of factors, including tumor type and subject ethnicity (100).

Viral diseases. Studies have shown that gene polymorphisms in the HO-1 promoter region are associated with the occurrence and progression of viral infectious diseases. Gill *et al* (48) demonstrated that individual HO-1 (GT)_n allele repeat length polymorphisms have a unique modifying effect on the risk of HIV-induced central nervous system neuroinflammation and associated neuropathy. The HO-1 S (GT)_n allele increases HO-1 promoter activity and exerts a neuroprotective function through inhibiting neuroimmune activation. Similarly, previous studies have shown that the HO-1 S (GT)_n allele sequence in African American populations reduces HIV-associated neuroinflammation and limits HIV-induced neurocognitive deficits (10,50). Therefore, therapeutic strategies that induce HO-1 expression should be able to reduce HIV-associated central nervous system inflammation and reduce the risk of HIV neurological disease development.

Kah *et al* (101) showed that inoculating mice with human hepatocytes containing the HO-1 S (GT)_n allele led to a decrease in the infection titer of hepatitis C virus (HCV) compared with mice inoculated with the HO-1 L (GT)_n allele. Therefore, HO-1-mediated HCV inhibition is (GT)_n polymorphism-dependent. In addition, it has been suggested that HO-1 promoter polymorphism may influence coronavirus COVID-19 disease severity, such as acute lung injury and thromboembolism. Therefore, the repeat length of the HO-1 (GT)_n allele in patients with severe COVID-19 should be investigated (102).

Other diseases. HO-1 gene promoter polymorphism has also been reported to be associated with neonatal hyperbilirubinemia (103), rheumatoid arthritis (12,104), pancreatitis (105), type II diabetes mellitus (106), heart disease (107) and other diseases to varying degrees. HO-1 carrying an S (GT)_n repeat gene promoter was found to be associated with a higher risk of neonatal hyperbilirubinemia (103). By contrast, carrying the S (GT)_n microsatellite allele was found to reduce the risk of rheumatoid arthritis and prevent the development of joint injury, whereas carrying the L (GT)_n microsatellite allele led to an increase in the susceptibility to rheumatoid arthritis and promoted the development of joint injury (12,104). For pancreatitis, the results of logistic regression analysis revealed that HO-1 containing the L (GT)_n allele doubled the risk of

pancreatic necrosis in patients with acute pancreatitis (105). However, in patients undergoing heart transplantation, (GT)_n polymorphism was not found to be associated with heart failure or patient survival. The researchers assumed that lower HO-1 activity in patients with L (GT)_n alleles might be compensated by other protective genes or enzymes (107). In addition, in a retrospective analysis of patients with type II diabetes, HO-1 T(-413)A SNP was significantly associated with the prevalence of low proteinuria, and patients with the TT genotype were more prone to develop proteinuria. Furthermore, *in vitro* experiments revealed that the promoter activity of HO-1 containing the A allele was higher than that of T allele (106). The AA genotype of HO-1 for T(-413)A SNP polymorphism was also found to reduce the incidence of ischemic heart disease, which might be associated with the high expression level of HO-1 (61).

5. Conclusions and prospects

As a stress-induced cytoprotective enzyme, HO-1 expression is regulated by a complex network, including transcription factors, cytoplasmic signaling pathways, post-translational modifications and genetic polymorphisms. The research of HO-1 induced expression primarily focuses on transcription factors. To treat a variety of diseases related to inflammation and immune regulation, screening small molecule HO-1 inducers that target transcription factors is the most commonly used method (108,109). However, this attempt at translational research was not successful and encountered great challenges. In addition to toxicity and bioavailability issues, HO-1 gene polymorphism in the population may also be an important reason for the difficulty of this translational study. Therefore, if the HO-1 gene polymorphism is added as a biomarker in clinical trials, it may improve the success rate of translational research. The current challenge is that the clinical results of the correlation between HO-1 gene polymorphism and disease are still controversial, especially due to the small sample sizes and inconsistent definition standards. On the other hand, the molecular mechanism underlying HO-1 polymorphism-mediated effects on HO-1 gene expression under disease conditions has not been fully revealed, which limits our understanding of the correlation between HO-1 gene polymorphisms and different diseases. Through the method of *in vitro* transient transfection, the relationship between (GT)_n repeats length and HO-1 expression level has been established at the cellular level; however, the research of (GT)_n repeat length effects on HO-1 expression at the animal level has not yet been reported. With the emergence of CRISPR technology, it is possible to construct HO-1 gene polymorphism transgenic mice. Future research should focus on exploring the molecular mechanisms by which HO-1 gene polymorphism and transcription factors coregulate HO-1 expression and affect disease using transgenic mouse systems. These investigations will provide further support for the development of targeted HO-1 reagents in different diseases.

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Authors' contributions

LLM and LS wrote and prepared the final version of the manuscript. YXW and BHS contributed to revising the manuscript. YFL and YLJ conceptualized the idea of the review. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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