Chapter 16
Heme Oxygenase 1(HO1): An Enzyme of Plant System and Its Role Against Various Abiotic Stresses

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Abstract Heme oxygenase 1 (HO1) is a well-known protector against oxidative stress in an animal system. In plant system, recently it's also well explored against different stresses. Heme oxygenase (HO) scavenges free heme released from heme proteins with the production of ferrous iron (Fe^{2+}), biliverdin-IXα (BV-IXα), and carbon monoxide (CO). HO illustrates functional diversity and engages in several functions. It regulates positively in antioxidant defense mechanism against various types of abiotic stress. Among all forms of HO, HO1 has been well explored against abiotic stresses as metal stress, salt stress, and drought stress; however, the differing roles of the other three HOs are still less identified. HO1 defects lead to reduced chlorophyll content. It delays gibberellin-triggered programmed cell death of aleurone layer due to drought stress by interacting with nitric oxide. HO1 along with nitric oxide and iron shows the long-distance signaling response to salt stress. Overall, the study helps to explore highlights on the recent studies related to plant HO research involving its antioxidant role against abiotic stresses.

Keywords Abiotic stress · Antioxidant defense mechanism · Drought stress · Heme oxygenase 1 (HO1) · Salt stress

1 Introduction

The role of heme oxygenase (HO, EC 1.14.99.3) and its location were firstly observed in an animal system. It binds to heme and forms a 1:1 complex (Kikuchi et al. 2005). In case of mammal system, heme oxygenase is a membrane-bound

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enzyme along with C-terminal hydrophobic tail. Two isoforms HO1 and HO2 of heme oxygenase have been observed (Yoshida et al. 1991). Davis et al. (2001) and Emborg et al. (2006) have reported that HOs consist of a small gene family with four members in the plant system. It has been categorized into two classes, HO1-like genes (including HO3 and HO4 of *Arabidopsis*) and HO2 genes, on the basis of amino acid sequence alignments in HO proteins. However, in cyanobacteria, algae, and higher plants, HO1 is soluble in nature (Unno et al. 2007). The report has revealed that HO1 is a single dense sphere consisting of mostly α-helix. Heme oxygenase has been recognized as a catalyst in plant system for the oxidation of heme to biliverdin IXα (BV), CO, and Fe^{+2} (Noriega et al. 2004; Shekhawat and Verma 2010; Shekhawat et al. 2011). In mammals, this BV IXα converts bilirubin IX α through bilirubin reductase enzyme (Ortiz de Montellano and Wilks 2001). Unno et al. (2007) have suggested that substrate heme adjusts in a sandwich-like structure between proximal and distal helix. The proximal end contains His 25 which is the proximal heme ligand involved in the binding of heme. Proximal and distal helices of substrate-free form of HO move freely with their conformation changes followed by heme-binding site opening. The fundamental structural folds of HO1 are conserved with different heme-binding pockets (Linly et al. 2006). In animal system, structure and size of HO1 are about comparable with few differences. Muramoto et al. (1999) have reported HO protein of molecular mass of 32.6 KDa having 55 amino acid chloroplast transit peptides in *Arabidopsis thaliana*. The main objective of this chapter is to highlight and be enlightened to the diversification in the regulatory role of HO1 along with its other members of the HO family in the plant cell. The main focus of this study is about the cross-talk between HO1 and other antioxidant enzymes or no enzymatic molecules.

2 Location of HO Gene Family in Plant Cell

The location of heme oxygenase 1 (HO1) in plant system has an interesting study after finding its presence in the plant system. The location of HO1 confirms more possible findings in regulatory roles in plant system. Due to the major regulatory role of HO1 in the phytochrome synthesis, it was suggested that the location of heme oxygenase is in the chloroplast. This fact was later on confirmed as well. It has been reported that HO1, among members of HO family, is located mainly in the stroma of chloroplast by using green fluorescent protein (GFP) reporter and immunoblot (Muramoto et al. 1999). Shekhawat and Verma (2010) have reported that HO1, a metalloprotein, catalyzes oxidative degradation of heme and protects against abiotic stress. HO1 catalyzes the heme degradation into biliverdin (BV IXα), carbon monoxide (CO), and ferrous ions (Fe^{+2}) (Fig. 16.1). Expression of HO1 responds to extensive cellular oxidative stress. Dixit et al. (2014) have suggested that oxidative stress elevates the level of reactive oxygen species (ROS), which causes the induction of HO1 expression. ROS mostly arises in the mitochondrion, connected with the leakage of partially reduced oxygen from the ETS under a normal and stressed

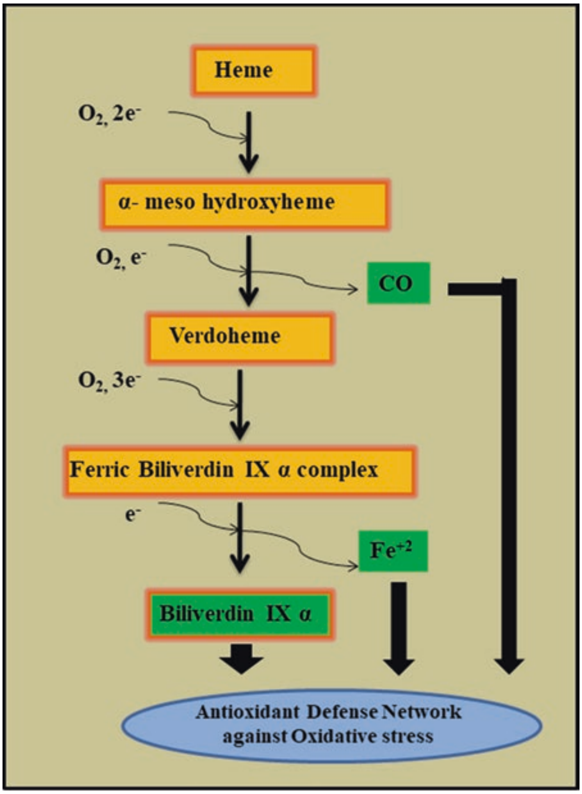

Fig. 16.1 Role of heme oxygenase 1 (HO1) in the degradation of heme and in antioxidant defense mechanism

condition. So, there is a possibility of co-localization of HO1 in the mitochondrion. Possible mitochondrial localization of HO1 might be on its inner membranous space because of its regulatory role in the synthesis of electron donor species. Subcellular localization of HO1 in chloroplast with mitochondrion has been confirmed in leaves of *Glycine max* L. (Dixit et al. 2014).

3 Regulatory Role of HO1 in Chromophore and Chlorophyll Synthesis

This is a well-known fact that active phytochrome leads to growth and photomorphogenic responses to red (R) and far-red light (FR) (Smith 1995; Quail 2002). In higher plants, HO1 has been discovered as the regulatory member in phytochrome–chromophore metabolism pathway. Holo-phytochrome protein is made up of PHY polypeptides and PφB chromophore. In case of PφB chromophore synthetic pathway, 5-aminolevulinic acid is the first precursor which is further converted into protoporphyrin IX followed by the formation of heme in the presence of ferrochelatase enzyme (Verma and Shekhawat 2013). Further, heme is transformed into biliverdin IXα by oxidative cleavage regulated by heme oxygenase 1 enzyme (HO1) (Terry et al. 1993). In this reaction step, heme oxygenase 1 makes use of reduced ferredoxin as an electron donor (Muramoto et al. 2002). Further, biliverdin IXα (BV IXα) is reduced into 3Z-PφB which regulated a ferredoxin-dependent PφB synthase enzyme (Frankenberg et al. 2001; Kohchi et al. 2001). Lastly, 3Z-PφB is isomerized into 3E-PφB by using phytochromobilin isomerase enzyme (Terry et al. 1995) 3E-PφB is then transported from chloroplast to the cytoplasm (Terry et al. 1993) and attaches to apophytochrome to make holo-phytochrome (Lagarias and Lagarias 1989).

Various reports confirmed the role of HO1 in chromophore synthesis by using mutant analysis of various plant species as mutant study of hy1 of *Arabidopsis thaliana*, yg-2 of tomato, and pcd-1 of pea (Terry and Kendrick 1999; Weller et al. 1996; Davis et al. 1999; Parks and Quail 1991). Parks and Quail (1991) and Davis et al. (1999) reported that hy1 mutant of *Arabidopsis* was not able to make PφB- and phytochrome-regulated responses. They confirmed it further by feeding these mutants with biliverdin IX α, which confirmed the negative effect of mutation resulting to lacking of heme oxygenase1 enzyme which converts heme into biliverdin IXα. Likewise, few other reports also suggested that mutant au and yg-2 of tomato are incapable to produce PφB, which is a resultant in plants with yellow-green phenotype (Terry et al. 2001) (Fig. 16.2).

Emborg et al. (2006) revealed that HO1, along with other members of the HO family in *Arabidopsis*, is vital for PφB synthesis and involved in the holo-phys assembly. Various mutant studies in plants reveal that HO is a key enzyme for phytochrome chromophore synthesis with involvement in the chlorophyll synthesis. hy1 and hy2 mutant of *Arabidopsis*, dark-grown au and yg-2 mutant of tomato, and pcd1 and pcd2 mutant of pea showed less Pchlide (precursor of chlorophyll) compared to their respective wild type. Beale and Weinstein (1991) and Cornah et al. (2003) revealed in their studies that there is a sharing pathway in between chlorophyll and phytochrome chromophore synthesis. In case of chlorophyll synthesis, Pchlide is formed by metal addition into protoporphyrin IX. In chlorophyll synthesis pathway, two steps are regulatory and rate-limiting. First is 5-aminolevulinic acid (5-ALA) formation from glutamate and second is metal insertion into protoporphyrin IX (Beale and Weinstein 1991; Cornah et al. 2003). Further, this Phclide forms chlorophyllide followed by chlorophyll synthesis. Terry and Kendrick (1999) revealed the indirect regulatory role of HO1 in chlorophyll synthesis by the mutant study of a yg-2 mutant of tomato. They observed that heme accumulated in mutant due to the inactivation of HO 1 enzyme which gives the origin of feedback inhibition for synthesis of 5-ALA. In spite of the plant system, feedback inhibition for 5-ALA synthesis through accumulated heme was reported in other systems also including cyanobacteria, green algae, and higher plants (Beale and Weinstein 1991; Castelfranco and Zeng 1991). However, Terry and Kendrick (1996, 1999) recommended in their report that inhibition of Pchlide synthesis is not connected to the inhibition of phytochrome. Some reports strongly support this opinion in which it

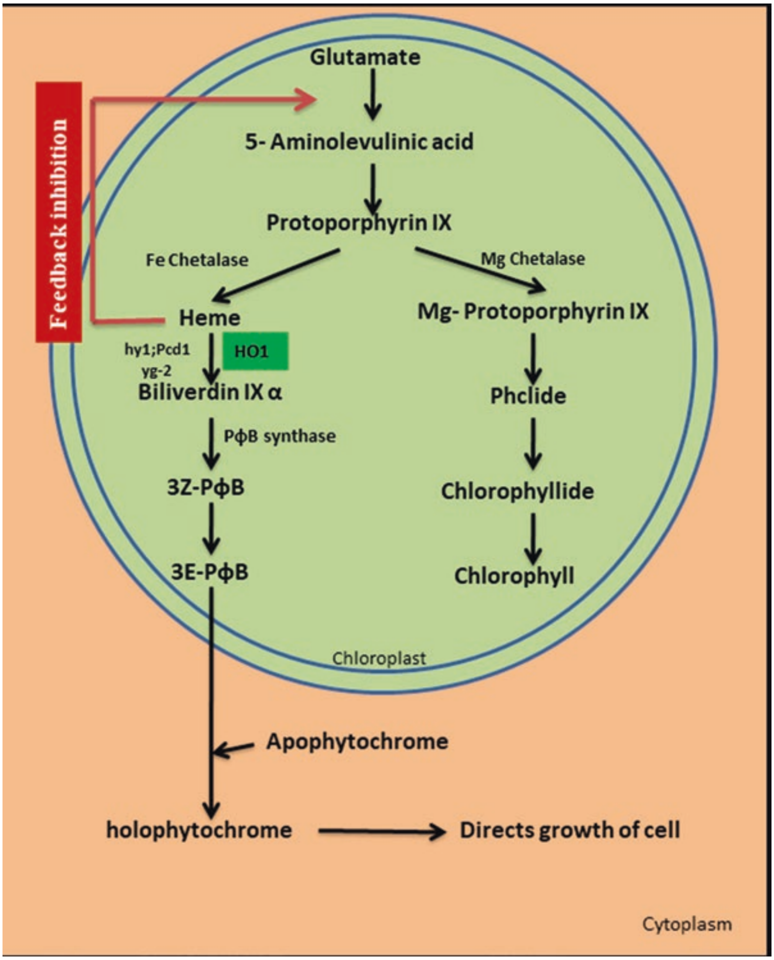

Fig. 16.2 Role of heme oxygenase 1 (HO1) in chromophore synthesis and indirect regulation of chlorophyll synthesis

was revealed that pale yellow-green phenotype had shown during their growth in several phytochrome mutant plants (Chory et al. 1989; Weller et al. 1996) (Table 16.1).

On the other hand, a severe reduction in Pchlide synthesis was reported in au and yg-2 mutant plants (Terry et al. 2001) which recommended that phytochrome also contributed to reduced Pchlide level in plant tissue (Terry et al. 2001). Hence, HO is a key enzyme for phytochrome chromophore synthesis and has an indirect regulatory role for chlorophyll synthesis with feedback inhibition of 5-ALA (Verma and Shekhawat 2013).

Table 16.1 Role of HO1 in different plant systems in response to various inducers/stress

Plants	Key function	Inducers/stress	Key references
Soybean (*Glycine max*)	Antioxidant responses	UV-B	Yannarelli et al. (2006)
Glycine max	Antioxidant responses	Cadmium	Noriega et al. (2004)
Glycine max	Antioxidant responses	Cadmium	Balestrasse et al. (2005, 2008)
Arabidopsis thaliana	Phytochrome–chromophore biosynthesis	HY1 locus	Davis (1999)
Alfalfa (*Medicago sativa*)	Antioxidant responses	Cadmium	Cui et al. (2011)
Glycine max	Antioxidant responses	Cadmium	Noriega et al. (2012)
Black mustard (*Brassica juncea* (L.) Czern.)	Antioxidant responses	Salt	Verma and Alam (2015)
Arabidopsis thaliana	Antioxidant responses	Salt, iron, and mercury	Wang et al. (2016)
Rice (*Oryza sativa* L.)	Delays gibberellin-induced programmed cell death	Drought	Wu et al. (2016)
Sunflower (*Helianthus annuus*)	Antioxidant responses	Salt/nitric oxide and iron	Singh and Bhatla (2016)
Rapeseed (*Brassica napus*)	Antioxidant responses along with defects lead to reduced chlorophyll	Various abiotic stress	Zhu (2017)
Cucumber (*Cucumis sativus*)	Adventitious root development and antioxidant responses	Drought	Chen et al. (2017)
Mung bean (*Vigna radiata*)	Antioxidant responses	Nickel–cadmium	Mahawar et al. (2017)
Oryza sativa L.	Antioxidant responses	Zinc	Chen et al. (2018)
Black mustard (*Brassica nigra*)	Antioxidant responses	Nano-silver	Amooaghaie et al. (2018)

4 Role of HO1 in Various Abiotic Stresses as an Antioxidant Enzyme

Heme oxygenase (HO, EC 1.14.99.3) enzyme is mainly responsible for stereospecific cleavage of heme and the heme oxidation to biliverdin IXα (BV), CO, and Fe^{+2} (Shekhawat and Verma 2010; Shekhawat et al. 2011). Many reports have supported the fact of HO's participation in plant system for cell protection mechanism against oxidative stress. In the response to stress conditions, HO has been acknowledged as a significant enzyme for ROS scavenging in both animals and plants (Ryter and Tyrrell 2000; Baranano et al. 2002; Noriega et al. 2004; Balestrasse et al. 2005, 2008). HO1 is directly not involved in these mechanisms. It shows involvement with its byproducts BV and BR as a component of the antioxidant defense mechanism in animals and plants (Stocker 1990; Ryter and Tyrrell 2000; Gonzales et al. 2002; Noriega et al. 2003, 2004; Balestrasse et al. 2008).

A lot of reports support HO1 as an antioxidant with all its byproducts of HO reaction. Balestrasse et al. (2005, 2008) suggested that HO1 was the main component of the antioxidant defense network in *Glycine max* L. plant against cadmium stress. In *Glycine max* L. under cadmium and salt stress, the level of BV increased because of the enhancement in the expression of HO1 in response to overcoming oxidative stress (Balestrasse et al. 2005, 2008; Zilli et al. 2009). Yannarelli et al. (2006) reported an elevation of HO1 activity against abiotic stress and enhancement of HO1 mRNA in *Glycine max* L. against UV-B stress. However, there are also some controversial reports. Various reports have revealed about the induction of HO1 by several factors such as its own substrate heme, NaCl, heavy metals, cadmium toxicity, UV-A and UV-B radiation, hyperoxia, and hypoxia (Maines and Kappas 1976; Maines 1988; Keyse and Tyrrell 1989; Tomaro et al. 1991; Noriega et al. 2004; Yannarelli et al. 2006; Balestrasse et al. 2008; Zilli et al. 2009) (Table 16.1).

According to previous reports, HOs have their contribution in only developmental biology like biosynthesis of phytochrome chromophore in plants (Muramoto et al. 2002; Terry et al. 2002; Kohchi et al. 2005; Emborg et al. 2006; Gohya et al. 2006). Analysis of the regulatory role of HO1 in Chinese cabbage, *Medicago sativa*, and wheat has also revealed that HO1 plays a significant role against various abiotic stresses in plant system (Cui et al. 2011; Fu et al. 2011; Jin et al. 2011; Xu et al. 2011). Noriega et al. (2012) suggested that HO1 is concerned in defense exerted by jasmonic acid against Cd stress in *Glycine max* roots.

In the past, the regulatory role of heme oxygenase 1 (HO1) under-reported as of the Antioxidant Defense Responses of *Brassica juncea* (L.) Czern. against Salt Stress Condition with treatment days dependant analysis and concentration-dependent analysis (Verma and Alam 2015; Verma et al. 2015). Wang (2016) revealed about characterization of AtHO1 promoter in reaction to salt stress, iron deficiency, and excess mercury exposure. Recently, Mahawar et al. (2017) has reported about positive role of HO1 in ROS quenching against Cd- and Ni-induced cytotoxicity in *Vigna radiata* L. Chen et al. (2018) has reported about the involvement of hemin through the HO1 system (along with its byproducts) against zinc stress in *Oryza sativa* L. with less zinc accumulation. Amooaghaie et al. (2018) have revealed about the role of HO1 activity and endogenous NO homeostasis which modulates the antioxidant defense system of *Brassica nigra* against stress induced due to nano-silver toxicity.

5 Cross-Talk Between HO1 Enzyme and Other Antioxidant Enzymes

In fact, for Pchlide, HO1 has a regulator role in antioxidant defense mechanism along with other antioxidants. Various reports revealed a pattern of expression of other antioxidant enzymes along with the elevated expression of HO1 (Balestrasse et al. 2005, 2008; Verma and Alam 2015; Verma et al. 2015). Balestrasse et al. (2008) who reported with their data propose that stimulation of CAT and HO1 occurred in nodules of soybean plants in the response to cell protection against oxidative damage due to cadmium stress. In *Brassica juncea* L. Czern., ascorbate peroxidase (APX), peroxidase (POD), and glutathione reductase (GR) expressed their highest activity at 150 mM NaCl concentration along with the upregulated expression of HO1 at the biochemical and molecular level (Verma et al. 2015). In *Vigna radiata*, HO1 activity was found to be highest against Cd stress and Ni stress with the increased activity of other antioxidant enzymes like CAT and APX (Mahawar et al. 2017). Chen et al. (2017) also reported about the possibility of CO byproduct of heme degradation by HO1; in H_2-induced adventitious root development under drought-induced stress, there is enhancement of leaf chlorophyll content and activation of antioxidant enzymes against oxidative stress. These reports suggest that HO1 has direct and indirect involvement through its products against oxidative stress and it plays as antioxidant enzyme.

6 Role of HO1 in Long-Distance Signaling Along with Other Molecules Against Abiotic Stress

Some reports have suggested and supported that HO1 has a role in long-distance signaling with other enzymatic and nonenzymatic molecules. As in past research, it has been identified that HO1 has indirect regulation in the synthesis of chlorophyll (Verma and Shekhawat 2013). This opinion was strongly supported by further research in *Brassica napus* by comparative sequencing analysis of *BnaC07.HO1* gene in wild and mutant species (Zhu et al. 2017).

On the other hand, few reports indicate about the role of HO1 along with nitric oxide and iron in the long-distance signaling response to salt stress (Singh and Bhatla 2016). It was suggested by this report that NO certainly alters HO1 activity in sunflower seedling cotyledons and there is a possible connection between endogenous NO, NaCl stress, and iron homeostasis by alteration of HO1 activity. HO1 also has a role in delaying gibberellin-triggered programmed cell death of aleurone layer due to drought stress by interacting with nitric oxide. It was suggested in evidence that GA regulates the expression of HO1 in germinating rice aleurone layers under drought stress condition (Wu et al. 2016). Santa-Cruz et al. (2017) also suggested that low methylation of HO1 promoter enhances the antioxidant activity against environmental stress. Their study has reported that some stress-related transcription factors are involved in HO1 upregulation against UV-B radiation and suggested a signaling link between TFs and HO1 expression. On the other hand, it's a well-known fact that accumulated proline plays a significant responsibility in the response of tolerance of plants against various abiotic stress. Gaseous signaling molecules such as a nitric oxide (NO) and carbon monoxide (CO), which are byproducts generated via HO1-regulated heme degradation process and hydrogen sulfide (H_2S), are involved in cell signaling. Somewhere, all these molecules regulate the accumulation of proline under abiotic-induced stress conditions (He and He 2017).

7 Conclusion

In plant system, heme oxygenase 1 (HO1) is a key enzyme for avoiding the negative and harmful effects of various abiotic stresses. By degradation of free heme, heme oxygenase (HO) generates byproducts such as ferrous iron (Fe^{2+}), biliverdin-IXα (BV-IXα), and carbon monoxide (CO). HO1, the member of HO family, shows diversification in regulatory role with its byproducts (BV-IXα, CO, and Fe^{2+}) and engages in various steps of antioxidant defense. In spite of the antioxidant role of HO1, it shows a role in chromophore synthesis, indirect regulation of chlorophyll, delayed programmed cell death, and lateral root development under abiotic stress. CO byproduct of HO1 also plays a role in H_2-induced adventitious root development under drought-induced stress by elevating the chlorophyll content and activation of antioxidant enzymes. Upregulation of HO1 activity has a connection with transcription factors to avoid the adverse effect of UV-B-induced stress. CO along with NO and H_2S has a signaling role in an enhancement of proline concentration under abiotic stress condition. This review concludes that HO1 has various regulatory roles in plant system as an antioxidant as well as a regulatory role in various signaling pathways and in developmental biology in regulating the chromophore, chlorophyll synthesis, and adventitious root development.

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