REVIEW PAPER

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Heme Oxygenase-1-Targeted Cancer Therapy: At the Crossroads of Cytoprotection and Tumour Progression

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ABSTRACT

Introduction. HO-1 is a stress-responsive enzyme involved in cellular protection against oxidative damage, inflammation, and tissue injury. However, in cancer, its cytoprotective functions may paradoxically support cancer progression, immune evasion, and therapy resistance.

Material and methods. This review explores current findings on HO-1's dual role in cancer biology. We analysed studies addressing its function in redox regulation, angiogenesis, immune modulation, iron metabolism, and its impact on treatment response. Particular focus was placed on HO-1's downstream metabolites (CO, biliverdin/bilirubin, and iron) and their influence on tumour development.

Results. HO-1 contributes to cellular defence by limiting reactive oxygen species and supporting DNA repair. However, its overexpression in tumours promotes survival signalling, angiogenesis (via VEGF and HIF-1α), metabolic reprogramming, and resistance to apoptosis and chemotherapy. Additionally, HO-1 regulates ferroptosis by modulating intracellular iron and lipid peroxidation. The Nrf2/HO-1 axis is frequently upregulated in tumours, enhancing antioxidant capacity and undermining therapeutic efficacy. Preclinical studies show that HO-1 inhibition—via gene silencing, small molecules, or combination with chemotherapy and photodynamic therapy—can restore treatment sensitivity and suppress tumour growth.

Conclusions. HO-1 plays a context-dependent, dual role in cancer as both a protector and promoter. Therapeutic targeting of HO-1 holds promise but requires precision to avoid disrupting its protective roles in normal tissues. Further research should aim to develop selective, tumour-specific HO-1 inhibitors and integrate them into combination treatment strategies.

Biological Role of HO-1

Cytoprotective Role of HO-1

HO-1 is a key component of the endogenous cellular defence system against oxidative stress and tissue injury, playing a multifaceted cytoprotective role in various physiological and pathological contexts. HO-1 is an inducible enzyme that catalyses the first and rate-limiting step in heme degradation, producing biliverdin, free iron, and

CO. Each of these products contributes to cellular homeostasis and protection. Biliverdin is rapidly converted into bilirubin, one of the most potent endogenous antioxidants, which neutralises ROS and prevents lipid peroxidation [1]. CO, despite its known toxicity at high levels, functions as a signalling molecule at physiological concentrations, inhibiting excessive inflammation and apoptosis via modulation of the mitogen-activated protein kinase (MAPK) and NF-κB pathways [1,2]. The free iron released during heme breakdown induces ferritin expression, thereby limiting Fenton reaction-mediated oxidative damage [3]. HO-1 expression is upregulated in response to diverse stressors, including hypoxia, pro-inflammatory cytokines, heavy metals, and UV radiation. Experimental models have demonstrated that elevated HO-1 levels protect tissues, including the liver, heart, kidneys, lungs, and central nervous system, from ischaemia-reperfusion injury, toxins, and inflammation [2]. *In vivo*, HO-1 overexpression reduces necrosis and apoptosis, limits leukocyte infiltration, and promotes tissue repair. HO-1 also modulates immune responses by influencing the function of T lymphocytes and macrophages, thereby fostering a tolerogenic immune profile and supporting regeneration mechanisms relevant to inflammatory diseases and transplant tolerance. Therefore, this effect is highly context-dependent; in specific cancer types, persistent HO-1 overexpression may paradoxically promote tumour cell survival and therapy resistance by enhancing antioxidant defences and inhibiting apoptosis [3]. Importantly, maintaining a balance in HO-1 activity is crucial, as chronic, uncontrolled overexpression of this enzyme has been observed in some cancers, where it enhances cancer cell survival and treatment resistance, posing a challenge for the development of targeted therapies [4].

In summary, HO-1 functions as a central cytoprotective mechanism by orchestrating antioxidant defence, immune modulation, and iron homeostasis. Its diverse biological effects make it a promising therapeutic target in conditions such as ischaemia-reperfusion injury, autoimmune disease, neurodegeneration, and cardiovascular pathology, while also demanding caution due to its potential pro-tumorigenic role, unlike earlier reviews published so far [5,6]. This work highlights novel insights into HO-1 regulation by exosomes, its dual role in ferroptosis, and its interplay with photodynamic therapy and immunotherapy, providing an updated perspective on the therapeutic potential of HO-1.

Anti-inflammatory effects

HO-1 and its metabolic byproducts exert antioxidant and anti-inflammatory effects by scavenging reactive oxygen species and limiting lipid peroxidation. Among its byproducts, carbon monoxide, generated during heme catabolism, acts as a signalling molecule that inhibits key inflammatory pathways such as NF-κB. This leads to reduced expression of pro-inflammatory cytokines, including IL-6, TNF-α, and IL-1β. A notable example of HO-1's anti-inflammatory relevance is andrographolide, a plant-derived compound that ameliorates ulcerative colitis by activating the Nrf2 (nuclear factor erythroid 2-related factor 2)/HO-1 pathway. Activation of Nrf2 leads to upregulation of HO-1, reduction of oxidative stress, and suppression of inflammatory cytokines, including IL-23, IL-17, and TNF-α. Andrographolide also restores levels of major antioxidant defence players like glutathione and superoxide dismutase. These effects are likely mediated through Nrf2 activation, rather than direct upregulation of antioxidant genes. These effects are reversed by the Nrf2 inhibitor ML385, confirming the central role of the Nrf2/HO-1 axis in mediating its protective action [7].

CO itself significantly contributes to immune modulation. Both endogenous CO production and pharmacological HO-1 induction suppress inflammatory cytokines (e.g., TNF-α, IL-17), while simultaneously increasing anti-inflammatory mediators, among which are IL-10 and IL-22 in colonic tissue. Inhibition of HO-1 attenuates these effects, highlighting CO's immunoregulatory potential [8]. Overall, HO-1 and its byproducts, such as CO, demonstrate potent anti-inflammatory and antioxidant actions by modulating key signalling pathways and cytokine production. This underscores its therapeutic relevance in inflammatory diseases and tissue protection.

Vascular regulation

HO-1 plays a critical role in regulating vascular dynamics within the tumour microenvironment, particularly in angiogenesis and vascular remodelling. As part of the cellular antioxidant defence system, HO-1 expression is strongly upregulated

under oxidative and inflammatory conditions, frequently observed in tumours. One of the key mechanisms involves the upregulation of vascular endothelial growth factor (VEGF) through interaction with the HIF-1α pathway under hypoxia. This promotes neovascularisation, facilitating tumour growth and nutrient supply. However, under specific contexts, excessive HO-1 expression can paradoxically suppress VEGF signalling, reflecting its context-dependent role in regulating the vascular system. HO-1-derived carbon monoxide promotes endothelial cell survival by inhibiting apoptosis through the NF-κB and MAPK pathways, while also downregulating adhesion molecules, including intercellular adhesion molecule 1 and vascular cell adhesion molecule 1. This dampens immune cell infiltration, creating an immunosuppressive microenvironment conducive to cancer progression [4].

Exosome-mediated signalling has emerged as another layer of HO-1. Tumour-derived exosomes can carry regulatory molecules such as microRNAs, long non-coding RNAs, and proteins that influence HO-1 expression and downstream signalling in recipient stromal and endothelial cell regulation. In prostate cancer, tumour-derived exosomes enriched with regulatory RNAs activate HO-1 pathways in neighbouring stromal or endothelial cells, promoting angiogenesis and resistance to anti-androgen therapy [9]. These findings highlight the importance of intercellular communication in reinforcing HO-1-mediated tumour adaptations. In line with these findings, HO-1 has been shown to modulate endothelial cell proliferation, migration, and tube formation, primarily through VEGF and activation of transcription factors such as NF-κB and Nrf2. While inhibition of HO-1 can effectively reduce angiogenesis and tumour growth in some settings, it may also impair endothelial integrity or increase oxidative stress in others.

Nevertheless, systemic HO-1 inhibition may impair endothelial function in normal tissues, increase oxidative stress, and compromise vascular perfusion, necessitating careful therapeutic targeting. Therefore, any therapeutic strategy targeting HO-1 must carefully consider the tumour type, vascular context, and potential systemic side effects [4].

Interestingly, cannabinoids, for example, cannabidiol (CBD), modulate vascular smooth muscle cell behaviour through HO-1 induction via ROS-dependent mechanisms. While HO-1 contributes to cytoprotection, CBD's antiproliferative and antimigratory effects appear to be both receptor-dependent and -independent. Notably, inhibition of HO-1 enhances the antiproliferative action of CBD, suggesting a complex interplay between ROS signalling and vascular regulation [10].

Finally, HO-1 metabolites—CO and bilirubin—contribute directly to vascular homeostasis. CO stimulates VEGF expression and endothelial proliferation. At the same time, bilirubin, with potent antioxidant activity, protects vascular structures and limits leukocyte adhesion and migration [11]. In summary, HO-1 plays a pivotal, highly context-dependent role in shaping tumour vasculature. It supports angiogenesis, preserves endothelial cell integrity, and contributes to immune evasion. This dual functionality makes HO-1 both a potential therapeutic ally and a risk factor, underscoring the need for precise, tumour-specific modulation in anticancer strategies.

Iron homeostasis

HO-1 is a key regulator of iron homeostasis, particularly within the tumour microenvironment, where it catalyses the degradation of heme into biliverdin, carbon monoxide, and free iron. This process not only supports cellular antioxidant defence but also influences several metabolic pathways linked to cancer progression and therapy response. By breaking down heme, HO-1 facilitates iron recycling within tissues. Although essential for local iron turnover, HO-1 is not the primary contributor to systemic iron needed for haematopoiesis. In HO-1 knockout mouse models, iron abnormally accumulates in the liver and kidneys while circulating levels decrease, leading to impaired systemic iron regulation [12]. Under normal conditions, intracellular iron is either exported via ferroportin or safely stored in ferritin. However, excessive HO-1 activity increases intracellular free iron, which can overwhelm detoxification systems and lead to reactive oxygen species production via Fenton reactions, ultimately driving lipid peroxidation and DNA damage. While HO-1 generally protects tumour cells from oxidative injury, under certain stress conditions, for instance, impaired ferritin buffering or increased ROS, excess iron can trigger ferroptosis, a form of regulated, iron-dependent cell death. Ferrop-

tosis is triggered by iron accumulation but also depends on the presence of polyunsaturated fatty acids (PUFAs) in membranes and the depletion of protective systems, such as glutathione or the glutathione peroxidase 4 enzyme [5]. This paradox highlights HO-1's dual role: promoting survival in early tumorigenesis by supporting redox homeostasis, yet potentially inducing cell death when iron accumulation exceeds protective thresholds. Notably, HO-1 is part of a broader antioxidant network regulated by transcription factors, particularly Nrf2, which is often activated in cancer. This activation frequently results from mutations in genes such as Kelch-like ECH-associated protein 1 (KEAP1) or nuclear factor, erythroid 2–like 2, leading to constitutive Nrf2 signalling that enhances antioxidant capacity and promotes the survival of cancer cells. Through the Nrf2/HO-1 axis, cancer cells can adapt to oxidative stress, enhance glutathione production, and resist chemotherapy or radiotherapy. However, this same system can be exploited therapeutically. Under certain conditions, HO-1-driven increases in intracellular iron may be redirected to promote ferroptosis, offering a strategic vulnerability in tumours resistant to conventional therapies [5].

In summary, HO-1 maintains a delicate balance between iron recycling and oxidative stress. While it protects against iron-mediated damage in normal physiology, its dysregulation in tumours may contribute to both survival and susceptibility. Understanding this balance is critical for leveraging HO-1 as a therapeutic target—either by enhancing its protective role or tipping it toward ferroptotic cell death in cancer therapy.

A dual role of HO-1 in cancer

HO-1 plays a complex and paradoxical role in cancer, acting as both a tumour suppressor and a promoter of cancer progression depending on the stage of tumorigenesis and the cellular context. This duality highlights the intricate interplay between oxidative stress, cellular metabolism, and survival mechanisms in cancer biology. This duality is also influenced by HO-1's subcellular localisation (cytosolic vs mitochondrial vs nuclear), stage-specific expression, and interactions with microenvironmental stressors such as hypoxia, inflammation, and immune cell activity [13].

HO-1 as a tumour suppressor

While HO-1 is often associated with cancer progression due to its antioxidant and cytoprotective functions, emerging evidence suggests that it can also exert tumour-suppressive effects, particularly in early stages of carcinogenesis. A key regulatory mechanism involves TRC8, an endoplasmic reticulum-associated E3 ubiquitin ligase with tumour-suppressive function. TRC8 targets HO-1 for ubiquitination and proteasomal degradation, limiting its accumulation and oncogenic potential. Loss of TRC8 leads to elevated HO-1 levels, which in turn enhance tumour cell proliferation, migration, and invasion. Conversely, reduced HO-1 expression is associated with increased oxidative stress, G2/M cell cycle arrest, and activation of DNA damage checkpoints—highlighting its role in redox homeostasis and genome surveillance [14]. These tumour-suppressive properties of HO-1 appear particularly relevant in the early phases of tumorigenesis, when genomic instability and oxidative damage are major drivers of malignant transformation. In addition, HO-1 and its metabolic product carbon monoxide contribute to genomic stability by mitigating ROS-induced damage and supporting DNA repair mechanisms. HO-1 has been shown to facilitate the activation of key DNA repair kinases such as ATM and ATR, which are essential for homologous recombination and non-homologous end joining. CO further enhances this protective effect by promoting efficient DNA repair, thereby reducing the accumulation of mutations that could drive malignant transformation or premature cellular senescence. Significantly, HO-1 and CO may modulate apoptotic responses to DNA damage, allowing time for repair before irreversible cell death is initiated [15]. Collectively, these findings suggest that HO-1 can function as a tumour suppressor by maintaining oxidative balance, promoting DNA integrity, and regulating cell cycle progression. Its interaction with tumour-suppressive regulators such as TRC8 underscores the relevance of post-translational control in limiting early tumour development.

HO-1 as a tumour promoter

Despite its well-established cytoprotective and anti-inflammatory functions, HO-1 is frequently overexpressed in various malignancies and is now widely recognised as a key pro-tumorigen-

ic factor. Emerging evidence demonstrates that HO-1 promotes cancer progression by shaping a microenvironment that favours immune evasion, metabolic adaptation, angiogenesis, metastasis, and resistance to therapy [5]. HO-1 facilitates cancer cell survival and proliferation primarily by modulating redox homeostasis and preserving mitochondrial integrity under stress. Its enzymatic degradation of heme produces biliverdin, bilirubin, CO, and ferrous iron—each of which contributes to tumorigenesis. Biliverdin and its reduced form, bilirubin, act as potent antioxidants that scavenge ROS, shielding tumour cells from oxidative damage and apoptosis [5]. CO, in turn, activates pro-survival pathways, including the MAPK cascade and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling, while promoting angiogenesis via soluble guanylate cyclase/cyclic guanosine monophosphate and VEGF pathways and supporting anti-apoptotic gene expression [4]. Beyond redox control, HO-1 reprograms iron metabolism in tumour cells. The enzymatic release of free iron from heme degradation increases intracellular Fe^{2+} levels, which can initially be sequestered by ferritin, serving an antioxidant buffering function. However, when iron accumulation exceeds cellular capacity, redox-active iron promotes the Fenton reaction, leading to ROS generation, DNA damage, genomic instability, and potentially oncogenic transformation [5]. HO-1 further contributes to immune evasion by regulating macrophage polarisation, suppressing dendritic cell maturation, and enhancing the activity of regulatory T cells. Its metabolic byproducts, CO and bilirubin, inhibit the expression of pro-inflammatory cytokines (e.g., IL-12, TNF-α) and promote the production of anti-inflammatory mediators such as IL-10 and TGF-β, thereby dampening effective immune surveillance [5]. Moreover, HO-1 has been shown to facilitate epithelial-to-mesenchymal transition, a critical mechanism underlying tumour invasion and metastasis, particularly in breast and prostate cancer models [13]. HO-1 also plays a pivotal role in the metabolic reprogramming of cancer cells. It induces glucose-6-phosphate dehydrogenase, the rate-limiting enzyme of the PPP, enhancing NADPH production and supporting glutathione regeneration. This shift not only strengthens antioxidant defences but also facilitates anabolic biosynthesis and tumour survival under metabolic stress.

Additionally, activation of the CO/cystathionine β-synthase pathway by HO-1 decreases 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase isoform 3 methylation, further diverting glucose flux into the PPP to sustain redox balance and proliferation, even under hypoxia [16]. The enzyme's contribution to therapy resistance is well documented. Overexpression of HO-1 in tumour cells confers protection against chemotherapy and radiotherapy by mitigating treatment-induced oxidative stress. This protection is mediated through Nrf2-dependent antioxidant responses, the upregulation of cyclin-dependent kinase inhibitor 1, and the suppression of caspase-3 activation [17,18]. Conversely, pharmacological or genetic inhibition of HO-1 has been shown to sensitise tumour cells to chemotherapeutic agents such as doxorubicin, cisplatin, and paclitaxel [13]. An especially intriguing aspect of HO-1 biology is its subcellular localisation. In some tumour types, notably prostate cancer, HO-1 is aberrantly translocated to the nucleus, where it loses its enzymatic activity but gains non-canonical regulatory functions. Nuclear HO-1 is associated with increased proliferation, resistance to apoptosis, enhanced oxidative metabolism, and recurrence, particularly under hypoxic conditions [13]. While CO may paradoxically sensitise tumour cells to genotoxic agents by increasing oxidative stress, HO-1 simultaneously protects surrounding healthy tissues from damage, highlighting the enzyme's context-dependent duality [19]. Altogether, these findings highlight the complexity of HO-1 as a potential tumour promoter. Its ability to modulate redox balance, immune function, metabolism, and therapeutic response makes it a compelling but challenging target in cancer therapy. Depending on the tumour type, cellular context, and disease stage, HO-1 may shift from a protective enzyme to an oncogenic driver, underscoring the importance of tumour-specific context when evaluating its role. Indeed, while some research groups emphasise the protective functions of HO-1 in preventing oxidative damage, maintaining genomic stability, and limiting early tumour initiation, others consistently report that its persistent overexpression promotes angiogenesis, immune evasion, and therapy resistance. This divergence reflects the highly context-dependent nature of HO-1 biology. In our view, the preponderance of recent evidence

indicates that in advanced malignancies, HO-1 functions predominantly as a tumour promoter. In contrast, its protective role appears more relevant in normal tissues and at the earliest stages of carcinogenesis.

Role of HO-1 in angiogenesis and Nrf2 pathway activation

HO-1 expression is strongly induced under hypoxic conditions, where it stabilises hypoxia-inducible factors (HIF-1α and HIF-2α), leading to upregulation of angiogenic mediators such as VEGF and COX-2. This promotes neovascularisation, fuelling tumour growth and metastasis. In contrast, under normoxia, HO-1 overexpression has a limited impact on angiogenesis, highlighting the importance of oxygen tension in its pro-angiogenic effects. Pharmacological inhibition of HO-1—for example, with ZnPP—has been shown to reduce VEGF levels and microvessel density both *in vitro* and *in vivo*, confirming its functional relevance [20,21]. The Nrf2/HO-1 axis, a key regulator of oxidative stress responses, also plays a central role in tumour angiogenesis. In hypoxia, Nrf2 activation leads to increased HO-1 expression and enhanced VEGF production. Compounds such as dextran sulphate and brusatol, which inhibit Nrf2, effectively suppress the expression of HO-1 and VEGF in gastric cancer models, thereby reducing their angiogenic potential. Conversely, tert-butylhydroquinone, a known Nrf2 activator, promotes angiogenesis—an effect that can be reversed by dextran sulphate [22]. These findings suggest that modulating Nrf2 signalling can significantly impact tumour vascularisation. Huang and coworkers [23] further demonstrated that hypoxia-induced Nrf2 activation increases HO-1 and VEGF levels, with CO serving as an intermediary pro-angiogenic signal. Analysis of tumour tissues revealed that Nrf2, HO-1, and VEGF expression positively correlate with microvessel density and tumour grade. The Cancer Genome Atlas datasets support these observations, showing co-expression of these genes in more aggressive cancers. Although Nrf2 is essential for maintaining redox homeostasis under physiological conditions, its persistent activation in tumours provides cancer cells with a survival advantage, enhancing resistance to chemotherapy and facilitating metastasis [24]. HO-1, as a downstream effector of Nrf2, contributes to this adaptation by inhibiting apoptosis and inducing cytoprotective autophagy. Pharmacological HO-1 inhibitors, such as ZnPP and SnPP, as well as gene-silencing strategies, have been shown to restore treatment sensitivity; however, their use is limited by potential off-target effects and the loss of HO-1's protective role in normal tissues [25]. In conclusion, the Nrf2/HO-1 signalling axis is a key driver of tumour angiogenesis under hypoxic stress, promoting vascular remodelling, immune evasion, and therapy resistance. Although targeting this pathway holds significant therapeutic promise, successful intervention will require context-specific approaches that minimise harm to normal cells while disrupting tumour-supportive angiogenesis.

Therapeutic implications of targeting HO-1

Given its dual role in cancer biology, HO-1 represents both a therapeutic target and a clinical challenge. Overexpression of HO-1 has been observed in various tumour types, where it contributes to proliferation, invasion, and metastasis via key oncogenic pathways, including MAPK/ERK and p38 signalling. Pharmacological inhibition of HO-1 reduces oxidative stress, lowers protein carbonylation, and suppresses tumour growth *in vitro* and *in vivo*. For example, the small-molecule inhibitor 2-[2-(4-bromophenyl)ethyl]-2-[(1H-imidazol-1-yl) methyl]-1,3-dioxolane hydrochloride has demonstrated significant anticancer activity and synergised with chemotherapy agents such as Taxol, enhancing tumour regression and reducing metastatic spread [26]. However, targeting HO-1 is complicated by its essential cytoprotective functions in healthy tissues. Systemic inhibition may disrupt antioxidant defence, provoke toxicity, and interfere with physiological immune regulation. Moreover, tumours may activate compensatory survival pathways when HO-1 is suppressed, limiting therapeutic effectiveness. An additional layer of complexity arises in cancers influenced by hormonal signalling, such as prostate cancer, where androgen deprivation has been associated with increased HO-1 expression, potentially undermining therapeutic response [26,27]. Gene-silencing strategies, such as small interfering RNA or short hairpin RNA, offer more specific approaches but often suffer from incomplete inhibition, off-target effects, and delivery challenges—especially when targeting tumour tissue while sparing vital organs like the

liver and kidneys. Despite these limitations, HO-1 inhibition remains a promising approach, particularly when combined with standard therapies, such as chemotherapy, radiotherapy, or immunotherapy. Preclinical studies have consistently shown that disrupting HO-1 signalling can restore chemosensitivity, enhance oxidative damage in tumour cells, and improve treatment outcomes [18,28,29].

In summary, effective targeting of HO-1 requires a context-specific and selective approach—one that suppresses its tumour-promoting activity while preserving protective functions in normal tissues. Future therapeutic strategies should aim to develop tumour-specific delivery systems, identify predictive biomarkers of HO-1 dependence, and explore rational combination therapies. Optimising HO-1 modulation could significantly improve therapeutic efficacy and expand the arsenal of targeted cancer treatments.

HO-1 inhibitors: mechanisms and therapeutic potential

Direct enzymatic inhibition

HO-1 inhibitors mainly block the catalytic activity of the enzyme, which involves the breakdown of heme to CO, biliverdin, and free iron. These inhibitors often act through competitive mechanisms, binding to the enzyme's active site and preventing heme interaction. Metalloporphyrins, for example, mimic the heme structure and bind to the catalytic domain of HO-1. By competing with heme, these inhibitors block enzymatic activity, leading to an accumulation of free heme, which acts as a pro-oxidant, inducing oxidative stress and apoptosis, especially in cancer cells. A critical structural feature for HO-1 inhibition is the presence of an azole nucleus (such as imidazole) that coordinates with the iron atom in the enzyme's active site. The therapeutic potential of these inhibitors lies in their ability to reverse HO-1's anti-apoptotic and pro-angiogenic effects, thereby reducing tumour proliferation, enhancing chemotherapy efficacy, and increasing oxidative stress within tumour cells [30]. It must, therefore, always be considered that direct enzymatic inhibitors competitively block HO-1's catalytic function, elevate intracellular heme, and promote pro-oxidant conditions that sensitise cancer cells to apoptosis and therapy.

Impact on downstream products of HO-1

Pharmacological inhibition of HO-1, such as with ZnPPIX or PEG-ZnPPIX, elevates oxidative stress and reduces angiogenesis by decreasing its downstream products. Bilirubin protects cells from oxidative damage, while CO, a key signalling molecule, contributes to tumour growth and treatment resistance by activating anti-apoptotic pathways and promoting angiogenesis. Additionally, free iron from heme breakdown can cause cytotoxicity via ROS formation if it accumulates excessively; however, cancer cells often upregulate iron regulation mechanisms to counteract this. HO-1 inhibition disrupts this balance, leading to increased oxidative stress and iron-mediated damage in cancer cells [6]. Blocking HO-1 -derived metabolites removes cytoprotective effects, weakens tumour antioxidant defences, and enhances oxidative stress and cytotoxicity.

Iron dysregulation and oxidative stress

HO-1 inhibition also targets tumour survival by disrupting iron homeostasis. Hyperactive HO-1 increases Fe^{2+} release from excessive heme degradation, producing hydroxyl radicals through the Fenton reaction and elevating iron-dependent oxidative stress. Tumours counteract this by increasing ferritin expression and activating survival pathways such as the Nrf2-Keap1 axis, protecting against ferroptosis. HO-1 inhibitors like ZnPPIX and SnPPIX can suppress the Nrf2-HO-1-FTH1 (FTH1 – ferritin heavy chain 1) pathway, increasing free iron and triggering lipid peroxidation and ferroptosis. Inhibition of HO-1 also upregulates transferrin receptor 1 (TFR1) and increases iron uptake, exacerbating iron dyshomeostasis and promoting cell death. Combining HO-1 suppression with ferroptosis-inducing drugs like Ras-selective lethal 3 MQC and Iristin further enhances therapeutic effects [31–34]. Targeting HO-1 disrupts iron regulation, triggers ferroptosis, and amplifies oxidative stress to overcome tumour resistance.

Future therapeutic directions and clinical perspectives

Inhibition of tumour growth and angiogenesis

HO-1 promotes tumour cell survival by supporting angiogenesis and counteracting oxidative

stress. Carbon monoxide, a product of heme degradation by HO-1, activates pro-survival pathways including the MAPK cascade and soluble guanylyl cyclase, facilitating proliferation and vascularisation. Concurrently, biliverdin and bilirubin function as potent antioxidants, scavenging reactive oxygen species that would otherwise impair tumour cell viability. Pharmacological or genetic inhibition of HO-1 disrupts these cytoprotective mechanisms, leading to reduced tumour cell proliferation, increased apoptosis, and suppression of angiogenic signalling. Studies have shown that HO-1 inhibition decreases cell viability in breast, melanoma, and pancreatic cancer models and can potentiate the efficacy of conventional chemotherapeutics such as paclitaxel or cisplatin [30,35]. Thus, HO-1 represents a promising target for impairing tumour vascular support and enhancing therapeutic responses.

Overcoming chemoresistance

HO-1 overexpression is frequently associated with resistance to chemotherapy, as tumour cells exploit its antioxidant and cytoprotective functions to withstand treatment-induced oxidative stress. Inhibiting HO-1 depletes intracellular antioxidant reserves, thereby resensitising tumour cells to chemotherapeutic agents. Combination therapies involving HO-1 inhibitors and cytotoxic drugs such as cisplatin or doxorubicin have been shown to enhance apoptosis and reduce tumour viability [6]. In breast carcinoma cell lines, HO-1 upregulation is linked to increased autophagy, which contributes to drug resistance. Silencing HO-1 expression or targeting upstream signalling pathways, such as PI3K/Akt, can inhibit autophagy and restore chemosensitivity [36]. Similar effects are reported in brain tumours, neuroblastoma, pancreatic ductal adenocarcinoma, and gastric cancer, where HO-1 inhibition enhances apoptosis, reduces immunosuppression, and improves prognosis [37–40]. Suppressing HO-1 disrupts tumour cell defence mechanisms, reverses chemoresistance, and enhances the cytotoxicity of anticancer drugs.

Inducing apoptosis in cancer cells

Inhibition of HO-1 promotes apoptosis through multiple mechanisms, including the accumulation of free heme, induction of oxidative stress, caspase activation, and mitochondrial dysfunction. HO-1 typically supports mitochondrial quality control and redox balance; however, its suppression compromises mitochondrial integrity, making tumour cells more susceptible to stress-induced apoptosis [25]. While HO-1 also influences mitochondrial quality control by regulating oxidative stress, its suppression can increase mitochondrial damage in tumour cells, compromising their survival under stress [41]. Interestingly, HO-1's dual role means that its inhibition can either prevent antioxidant protection or induce ferroptosis by increasing lipid peroxidation.

Indeed, HO-1 has emerged as a critical regulator of ferroptosis—a distinct, iron-dependent form of programmed cell death marked by lipid peroxidation. The enzymatic activity of HO-1 breaks down heme into free ferrous iron (Fe^{2+}), biliverdin, and carbon monoxide. Elevated intracellular iron levels can catalyse the Fenton reaction, enhancing ROS production and triggering lipid peroxidation, which are hallmarks of ferroptosis. Activation of HO-1 (e.g., via haemin or carbon monoxide-releasing molecules) sensitises cancer cells to ferroptosis inducers such as erastin. In contrast, pharmacological inhibition of HO-1 (e.g., with ZnPP) reduces ferroptotic cell death, suggesting a dose- and context-dependent role of HO-1 in this pathway. While HO-1-derived biliverdin and bilirubin serve as antioxidants that may mitigate ferroptotic damage, excessive HO-1 activity can overwhelm redox buffering systems and promote cell death. Moreover, the transcriptional regulation of HO-1 by Nrf2 links oxidative stress to ferroptosis: Nrf2 activation induces HO-1 expression in response to redox imbalance, which paradoxically can increase cellular susceptibility to iron-driven lipid peroxidation in cancer cells. The subcellular localisation of HO-1 further modulates its function—mitochondrial HO-1 contributes to redox regulation and cellular adaptation to stress, whereas nuclear HO-1 is associated with aggressive tumour behaviour and poor prognosis [13]. Thus, modulation of HO-1 activity—whether to promote apoptosis via mitochondrial damage or to induce ferroptosis through iron overload—represents a potent therapeutic avenue. Collectively, these mechanisms demonstrate how HO-1 inhibition selectively impairs tumour cell survival pathways, providing an effective strategy for inducing programmed cell death in cancer cells.

Combination with immunotherapy and PDT

Photodynamic therapy (PDT) relies on the generation of ROS to eliminate tumour cells. However, HO-1 mitigates PDT-induced oxidative damage by neutralising ROS and promoting survival signalling, thus reducing treatment efficacy. Inhibitors such as ZnPPIX have been shown to sensitise tumours to PDT by lowering the levels of cytoprotective HO-1 metabolites [6,42]. Recent advances in nanomedicine and combination therapies aim to overcome this limitation. For example, ZnPP@FQOS (a tumour microenvironment-responsive organosilica hybrid nanoformulation) enhances ROS production, downregulates HO-1, and stimulates dendritic cell maturation and cytotoxic T lymphocyte activation, thereby augmenting both PDT and immunotherapy effects [43]. Combining HO-1 inhibition with PDT and immunotherapy sensitises tumours to oxidative damage and enhances immune-mediated tumour clearance.

In summary, therapeutic strategies targeting HO-1 can inhibit tumour growth, overcome chemoresistance, induce apoptosis, and improve the efficacy of adjunct therapies, including immunotherapy and PDT. However, the dual nature of HO-1 necessitates a context-specific approach that maximises antitumor effects while minimising potential harm to normal tissues. Ongoing research into selective inhibitors and tumour-targeted delivery systems will be critical for translating these insights into effective clinical interventions (see **Table 1**).

Divergent therapeutic perspectives on HO-1

Different groups have reached contrasting conclusions regarding the therapeutic targeting of HO-1. While some suggest that HO-1 induction may confer beneficial anti-inflammatory and cytoprotective effects, others argue that inhibition is necessary to overcome therapy resistance and sensitise tumours to chemotherapy, radiotherapy, or photodynamic therapy. Based on the integration of recent preclinical evidence, we consider selective HO-1 inhibition, particularly in combination with other therapeutic modalities, to be the more promising strategy in the oncological setting.

Table 1. Dual role of HO-1: protective in normal cells vs. tumour-promoting in cancer cells.

Mechanism	Role of HO-1 in Normal Cells	Role of HO-1 in Cancer Cells
Redox homeostasis and ROS scavenging	Maintains redox homeostasis and eliminates ROS, preventing oxidative DNA damage and mutations that could lead to cancer.	Neutralises ROS generated during chemotherapy/radiotherapy, reducing DNA damage and enabling resistance.
DNA repair	Activated in response to ROS to promote DNA repair and genome stability via pathways such as ATM/ATR and BRCA1.	Enhances DNA repair after therapy-induced damage, contributing to chemoresistance and radioresistance.
Cytoprotective and anti-inflammatory functions	Reduces oxidative stress and inflammation, supports mitochondrial integrity, and promotes cell survival.	Promotes tumour cell survival under stress, including drug-induced stress.
Antioxidant heme metabolites	Biliverdin and bilirubin scavenge ROS; CO mediates anti-inflammatory signalling and cytoprotection.	CO signalling promotes cell survival, inhibits apoptosis, and facilitates treatment resistance.
Role of HO-1 in Cancer Cells only		
Therapy resistance	Overexpression correlates with poor prognosis and therapy resistance; it increases after exposure to therapy-induced ROS.	
Autophagy regulation	Regulates autophagy via Beclin-1, p62, LC3B-I/II, aiding in survival and resistance.	
Anti-apoptotic effects	Increases anti-apoptotic proteins (e.g., Bcl-xL), suppresses apoptotic pathways (e.g., caspase-3), promotes survival in response to targeted drugs (e.g., rapamycin, sorafenib).	
Proliferation, angiogenesis, metastasis	Supports mitochondrial biogenesis and metabolic adaptation; promotes angiogenesis via VEGF and enhances metastasis.	
Subcellular localization	Nuclear HO-1 is associated with malignancy and poor prognosis; mitochondrial HO-1 supports metabolic flexibility and redox control.	

ATM, ataxia telangiectasia mutated; ATR, ATM- and Rad3-related; BRCA1, breast cancer 1, early onset; Beclin-1, Bcl-2–interacting protein 1; p62, sequestosome 1 (SQSTM1); LC3B-I/II, microtubule-associated protein 1 light chain 3 beta-I/II; Bcl-xL, B-cell lymphoma-extra large; caspase-3, cysteine-aspartic acid protease-3

Conclusion

HO-1 is a paradoxical regulator in cancer biology. It simultaneously exerts cytoprotective, antioxidant, anti-apoptotic, and immunomodulatory functions that can either safeguard tissues or promote cancer progression. The long-standing debate over whether HO-1 acts as a "friend or foe" in tumours has been discussed in previous reviews [5,6]. Our synthesis builds upon this discussion by incorporating recent advances that substantially refine this duality. In particular, we highlight novel aspects such as the contribution of HO-1 to ferroptosis, the impact of its subcellular localisation (nuclear versus mitochondrial HO-1) on tumour aggressiveness and therapy response, and the regulation of HO-1 signalling through tumour-derived exosomes. These mechanisms provide additional layers of complexity not fully addressed in earlier literature and point to emerging opportunities for therapeutic exploitation.

Significantly, the interpretation of HO-1's role depends heavily on tumour type, disease stage, and microenvironmental context. While some groups emphasise the protective effects of limiting oxidative damage and maintaining genomic stability, others demonstrate that persistent HO-1 overexpression promotes angiogenesis, immune evasion, and therapy resistance. Based on the weight of current evidence, we consider sustained HO-1 activity in advanced malignancies to be predominantly tumour-promoting. In contrast, its physiological role in normal tissues and early carcinogenesis remains protective. This context-specific duality must therefore inform future therapeutic strategies.

Looking ahead, several directions appear particularly promising. First, selective inhibition of HO-1 should be investigated as a means to overcome drug resistance, enhance ferroptosis, and improve the efficacy of chemotherapies and radiotherapies. Second, combining HO-1 modulation with photodynamic therapy and immunotherapy represents a timely avenue, supported by recent nanomedicine-based approaches. Third, understanding the non-canonical functions of nuclear HO-1 and its role in metabolic reprogramming may open new therapeutic frontiers. Finally, the identification of biomarkers predicting tumour dependence on HO-1 could enable patient stratification and personalised interventions. In summary, while the dual role of HO-1 has been recognised for more than a decade, our review distinguishes itself by highlighting cutting-edge insights into ferroptosis, exosomal signalling, subcellular localisation, and combined treatment approaches. We conclude that selective and context-specific inhibition of HO-1 in advanced cancers holds the most significant translational potential, whereas its activation may remain advantageous in non-malignant pathologies. Fully exploiting HO-1 as a therapeutic target will require reconciling divergent observations. Still, we believe that its integration into rational combination strategies offers one of the most promising directions for the future of cancer therapy.

Glossary

HO-1, heme oxygenase-1; CO, carbon monoxide; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; HIF-1a, hypoxia-inducible factor 1-alpha; VEGF, vascular endothelial growth factor; FTH1, ferritin heavy chain 1; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; PPP, pentose phosphate pathway; CLs, cytotoxic T lymphocytes; DCs, dendritic cells; PD-L1, programmed death-ligand 1; OB-24, 2-[2-(4-bromophenyl)ethyl]-2-[(1H-imidazol-1-yl)methyl]-1,3-dioxolane hydrochloride; ZnPP, zinc protoporphyrin IX; SnPP, tin protoporphyrin IX; PDT, photodynamic therapy; TNF-α, tumour necrosis factor alpha; IL-10, interleukin-10; IL-6, interleukin-6.

Disclosures

The author's contribution
Both authors (MR and MM) contributed equally to the conceptualisation, literature search, analysis and interpretation of the data, as well as to writing, reviewing and editing the manuscript. Both authors have read and approved the final version of the manuscript.

Conflict of interest statement
The authors declare no conflict of interest.

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