REVIEW ARTICLE

Targeting heme oxygenase-1/carbon monoxide for therapeutic modulation of inflammation

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The heme oxygenase-1 (HO-1) enzyme system remains an attractive therapeutic target for the treatment of inflammatory conditions. HO-1, a cellular stress protein, serves a vital metabolic function as the rate-limiting step in the degradation of heme to generate carbon monoxide (CO), iron, and biliverdin-IXα (BV), among which the last one is converted to bilirubin-IXα (BR). HO-1 may function as a pleiotropic regulator of inflammatory signaling programs through the generation of its biologically active end products, namely CO and BV/BR. CO, when applied exogenously, can affect apoptotic, proliferative, and inflammatory cellular programs. Specifically, CO can modulate the production of proinflammatory or anti-inflammatory cytokines and mediators. HO-1/CO may also have immunomodulatory effects with respect to regulating the functions of antigen-presenting cells, dendritic cells, and regulatory T cells. Therapeutic strategies to modulate HO-1 in disease include the application of natural-inducing compounds and gene therapy approaches for the targeted genetic overexpression or knockdown of HO-1. Several compounds have been used therapeutically to inhibit HO activity, including competitive inhibitors of the metalloporphyrin series or noncompetitive isoform-selective derivatives of imidazole-dioxolanes. The end products of HO activity, BV/BR, and CO may be used therapeutically as pharmacologic treatments. CO may be applied by inhalation or through the use of CO-releasing molecules. This review will discuss HO-1 as a therapeutic target in diseases involving inflammation, including lung and vascular injury, sepsis, ischemia/reperfusion injury, and transplant rejection. (Translational Research 2015;■:1–27)

Abbreviations: ALI = acute lung injury; APCs = antigen-presenting cells; ARE = antioxidant responsive element; Bach1 = BTB and CNC homolog 1; BAL = bronchoalveolar lavage; BR = bilirubin-IXα; BV = biliverdin-IXα; BVR = biliverdin reductase; CO = carbon monoxide; CO-Hb = carboxyhemoglobin; COPD = chronic obstructive pulmonary disease; CORM = CO-releasing molecule; CPR = cytochrome p-450 reductase; DCs = dendritic cells; DMF = dimethyl fumarate; EGR-1 = early growth response protein 1; ERK1/2 = extracellular regulated protein kinase 1/2; FoxP3 = forkhead box P3; HO = heme oxygenase; HFD = high-fat diet; HO-1 = heme oxygenase-1; HO-2 = heme oxygenase-2; HMGB1 = high-mobility group box 1; HSF-1 = heat shock factor 1; IFN-β = interferon beta; IL = interleukin; iNOS = inducible nitric oxide synthase; I/R = ischemia/reperfusion; JNK = c-Jun NH_2-terminal kinase; Keap1 = kelch-like ECH-associated protein; LPS = lipopolysaccharide; MAPK = mitogen-activated protein kinase; miR = microRNA;

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MV = mechanical ventilation; NADH = nicotinamide adenine dinucleotide, reduced form; NADPH = nicotinamide adenine dinucleotide phosphate, reduced form; NLRP3 = NOD-, leucine rich region- and pyrin domain-containing 3; Nrf2 = nuclear factor erythroid 2–related factor 2; p38 MAPK = p38 mitogen-activated protein kinase; PI3K/Akt = phosphatidylinositol-3-kinase/Akt; PhotoCORMs = photoactivatable carbon monoxide-releasing molecules; ROS = reactive oxygen species; SCD = sickle cell disease; SMC = smooth muscle cells; SNP = small nucleotide polymorphism; SnPPIX = tin protoporphyrin IX; SPM = specialized proresolving mediators; StRE = stress-responsive element; TLR4 = toll-like receptor 4; Treg = regulatory T lymphocyte; VILI = ventilator-induced lung injury

INTRODUCTION

The heme oxygenase (HO) enzyme system continues to intrigue researchers across the spectrum of biological sciences from those engaged in the study of basic metabolism and enzymology to those investigating the pathogenesis of human disease with the ultimate goal of developing molecular medicine.[1] HO provides an essential enzymatic activity by catalyzing the rate-limiting step in the oxidative catabolism of heme in a reaction that generates carbon monoxide (CO), ferrous iron, and biliverdin-IXα (BV), among which the last one is converted to bilirubin-IXα (BR) (Fig 1).[2,3] Heme, the natural substrate and enzyme cofactor for HO, serves as a key mediator of many vital biological processes including oxygen transport and delivery to tissues, peroxide metabolism, cell signaling, xenobiotic detoxification, and mitochondrial bioenergetics. Thus, HO enzymes may fulfill a crucial metabolic function by regulating heme bioavailability and turnover in cells and tissues.[4] In addition to this well-characterized metabolic function, heme oxygenase-1 (HO-1), the inducible form of HO, has gained recognition as a ubiquitous 32-kDa stress protein whose expression is highly upregulated in mammalian cells or tissues during cellular stress.[5,6]

In mammals, the gene(s) that encode HO-1 (HMOX1 in humans, *Hmox1* in rodents) are highly transcriptionally regulated by injurious stimuli. In addition to the natural substrate heme and oxidizing cellular stress, such as generated by ultraviolet-A radiation, hydrogen peroxide (H_2O_2), and redox-cycling compounds, HO-1 responds to induction by a multiplicity of chemical and physical agents, including heat shock (in rodents), fluctuations in oxygen tension, nitric oxide, thiol-reactive substances, heavy metals, cytokines, and natural phytochemicals (see Table I for summary).[5-22] Increased HO-1 expression in tissue is commonly associated with increased inflammation or oxidative stress as exemplified by models of acute lung injury (ALI) and ischemia/reperfusion (I/R) injury.[22-24]

The central importance of HO-1 in human physiology and tissue homeostasis is accentuated by studies of naturally occurring genetic deficiency of HO-1 in humans. A patient with human HO-1 deficiency presented with severe hemolytic anemia, endothelial degradation, reduced serum bilirubin, renal and hepatic iron accumulation, and a proinflammatory phenotype.[25] Similarly, HO-1 gene-deleted mice ($Hmox1^{-/-}$) displayed increased inflammation accompanied by tissue iron accumulation, whereas cells isolated from these animals displayed increased susceptibility to oxidative stress.[26,27] Several studies, which have used $Hmox1^{-/-}$ mice or HO-1 transgenic mice, have demonstrated the tissue protective properties of HO-1 in mouse models of cardiovascular, pulmonary, cardiac, or skin injury and disease (see Table II for summary).[28-37] Despite these observations, deleterious consequences of HO-1 or HO-2 overexpression have been reported in vitro and in vivo associated with toxic levels of iron accumulation.[38-43]

The mechanisms by which HO-1 expression is associated with context-specific cytoprotection remain incompletely clear, but may reside in the combined effects of the removal of heme (a pro-oxidant iron chelate) with the enzymatic generation of biologically active end products from heme catabolism.[43] This hypothesis has provided the basis for the development of new fields focused on the pharmacologic delivery of HO-1 reaction products. In this regard, application of CO has demonstrated tissue protective effects in models of acute inflammation and organ injury.[28,44] These studies, using inhaled CO gas, include endotoxemia,[45-47] hyperoxia-induced ALI,[48,49] ventilator-induced lung injury (VILI),[50-52] sepsis and pneumonia,[53-55] I/R injury,[56,57] vascular injury and disease,[58-60] and organ transplantation[58,61-83] (see Table III for representative summary). The protective effects observed in these models were attributed to the effects of CO on apoptosis, cell proliferation, inflammation, and immunomodulation.[28,44] Similarly, the pharmacologic applications of BV or BR, enzymatic products of heme metabolism, have shown protective effects in models of organ injury and transplantation.[63,67,81,84-86]

In addition to pleiotropic cellular effects of HO-1, including reported effects on the regulation of