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Myeloid heme oxygenase-1: a new therapeutic target in anti-inflammation

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Myeloid cells and inflammation
- *3.1. Functional of granulocytes in inflammation*
- *3.2. Functional of macrophages in inflammation*
- *3.3. Functional of monocytes in inflammation*
- *3.4. Function of DCs in inflammation*

4. Role of myeloid HO-1 in the pathological process of inflammation
- *4.1. Role of myeloid HO-1 effects on NKT and NK cells*
- *4.2. Role of myeloid HO-1 effects on T cells*
- *4.3. Role of myeloid HO-1 effects on B cells*
- *4.4. Molecular mechanisms of myeloid HO-1 gene regulation in inflammation*
- *4.5. Protective role of myeloid HO-1 in inflammation diseases*
- *4.6. Myeloid HO-1 bridges a crosstalk between autophagy, apoptosis, oxidative stress, and inflammation*

5. Compounds as myeloid HO-1 expression inducer
- *5.1. Aminolevulinic acid (5-ALA)*
- *5.2. Dihydroquercetin (DHQ)*

6. Summary and conclusion
7. Acknowledgments
8. References

1. ABSTRACT

An increasing amount of evidence reveals that an orchestrated interplay between myeloid subpopulations in the hematopoietic system plays a significant role in supporting normal functions of the immune system and facilitating homeostatic restoration upon exogenous or endogenous insults. Heme oxygenase-1 (HO-1), a microsomal enzyme discovered decades ago, can metabolize pro-oxidant heme into biliverdin, free iron, and carbon monoxide. This enzymatic reaction produces biological materials, contributing to major immunomodulatory effects. Specifically, HO-1 expression in myeloid cells has been generally acknowledged to drive potent anti-inflammatory and immunosuppressive responses. In this review, the authors focused on elucidating the potential mechanisms underlying myeloid HO-mediated immunomodulation phenotypes, and discussed the potential application of myeloid-specific HO-1 induction as an anti-inflammation therapeutic strategy.

2. INTRODUCTION

When the immune system is activated after a detrimental attack, an organism must be able to balance the stimulated proinflammatory and corresponding anti-inflammatory processes to achieve homeostasis for maintaining normal physiologic status. This is significant as the production of proinflammatory factors is crucial for successfully eliminating the infective

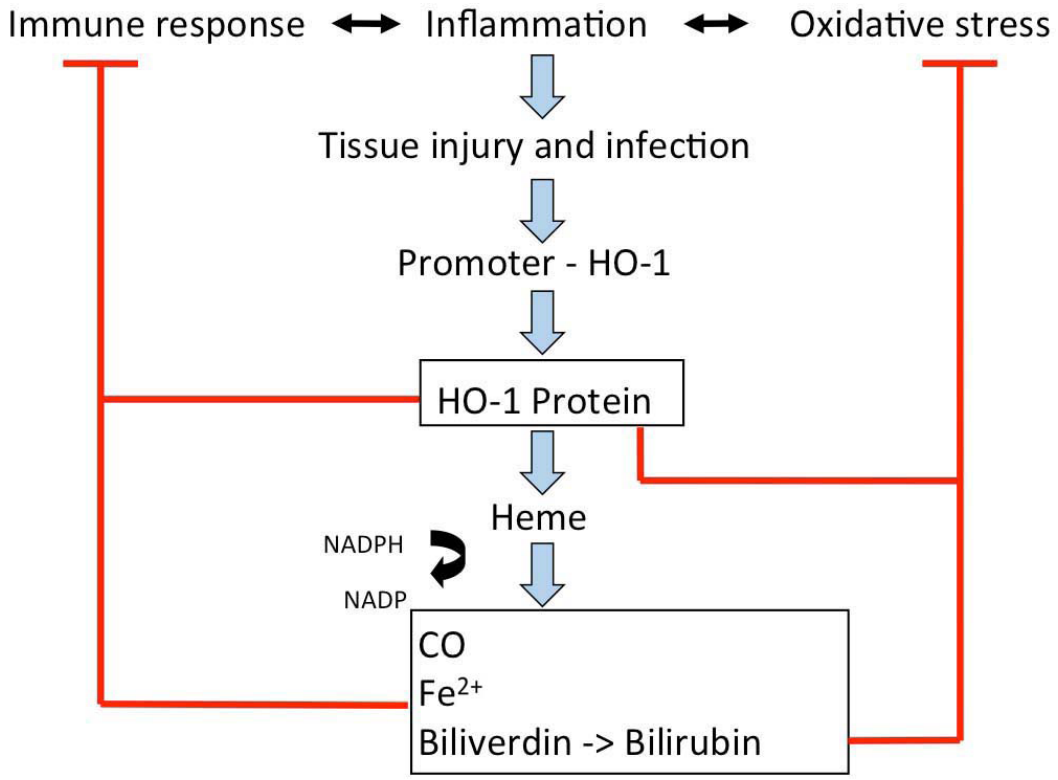

Figure 1. HO-1 metabolizes heme. The HO-1 promoter has elements for many transcription factors and responds to heme. These induce HO-1 protein, which then metabolizes carbon monoxide, iron, and biliverdin (which is converted into bilirubin in a coupled reaction). HO-1 and the three by-products appear to have anti-inflammatory and anti-oxidant properties. NADP, nicotinamide adenine dinucleotide phosphate; NADPH, β-nicotinamide adenine dinucleotide 2'-phosphate reduced tetrasodium salt.

agents, whereas the restoration of homeostasis is necessary for minimizing immune system disorders associated with pathology (1). Accumulating studies have demonstrated that the coordinated interplay between myeloid cells (e.g. macrophages, neutrophils, monocytes, and dendritic cells) is required for maintaining this delicate yet important physiologic balance (2, 3).

Heme oxygenase-1 (HO-1) is a microsomal enzyme catabolizing pro-oxidant heme into biliverdin, free iron, and carbon monoxide (CO) (4, 5). These by-products appear to have potent cytoprotective properties (6) as shown in Figure 1. HO-1 expression is ubiquitously induced as a response to diverse stimuli related to oxidative stress and inflammation, including cytokines, hypoxia, hyperoxia, heavy metals, nitric oxide (NO), heat shock, thiol-reactive substances, hydrogen peroxide, and shear stress, where this expression activates or suppresses cell-intrinsic pathways (7, 8). Moreover, increasing evidence indicates that HO-1 derived from myeloid cells contributes to the pathogenesis of numerous virus infections and alters responses of infectious and organ-specific autoimmune diseases (5, 9). This review highlights the current progress on: i) the association between myeloid cells and inflammation; ii) the contribution of myeloid HO-1 to immune responses; iii) the mechanisms underlying myeloid HO-1 regulation and this enzyme's capability for treating immune disorders.

3. MYELOID CELLS AND INFLAMMATION

Myeloid cells include four subgroups, namely, granulocytes, monocytes, macrophages, and dendritic cells (DCs) (10). They can be promptly recruited to the infected or damaged sites through peripheral or lymphatic trafficking, with the facilitation of a number of different chemokine receptors (11-14). The infiltrated myeloid cells are activated for phagocytosis and secrete a diverse variety of inflammatory mediators to realize functional plasticity in immunity (15-17).

3.1. Functional of granulocytes in inflammation

Granulocytes, a differentiated lineage derived from hematopoietic stem cells in bone marrow (BM), are the most abundant component of the myeloid population. They include four subcategories, namely, neutrophils, eosinophils, basophils, and mast cells. Neutrophils are generated in high number in BM and can be triggered for activation while in circulation through communication with signals from the resident

macrophages at the infected or injured site (17). Eosinophils, in addition to localizing in BM, are also found in various organs (e.g., gastrointestinal tract, heart, and lung). They are important in forming an immune barrier against parasites and allergens, and therefore support physiologic homeostasis (18). Basophils and mast cells can contribute to the development and progression of Type 2 T helper (Th2) cytokine-mediated inflammation (19). They are able to release potent inflammatory mediators, such as proteases, histamine, heparin, and other molecules, which can initiate and modulate an inflammatory response by acting on various tissues and cells (20).

3.2. Functional of macrophages in inflammation

Macrophages perform diverse roles in homeostasis and disease progression that can involve developmental integrity, tissue repair machinery, and immune modulations. These functions of macrophages could be executed in a well-controlled manner, and could involve multilevel cellular responses. For instance, recognition of pathogen-associated molecular patterns (PAMPs), phagocytic clearance, and cytokine secretion are significant components of macrophage-mediated responses. The accumulative results could further lead to recruitment of other types of cells, triggering a systematic immune response. In general, macrophages can elicit inflammation, scavenge tissues, and actively regulate immune responses. Notably, the primary function of macrophages is to initiate adaptive immune responses by presenting pathogen-derived antigens to T cells (21). Moreover, macrophages are one major cell type responsible for efferocytosis, the process of engulfing and destroying dying cells, thus releasing harmful intracellular biomaterials to trigger inflammation that could lead to autoimmunity (22, 23).

3.3. Functional of monocytes in inflammation

Monocytes, an important component of the innate immune system, are among the first batches of cell types to sense and respond to the local insults by migrating from the peripheral blood to the infected site and differentiating into tissue macrophages and dendritic cells to take part in the immune response. Endowed with dualism due to their heterogeneity and functional plasticity, monocytes are able to exert versatile immune functions during the different stages of immunity (24). They can produce proinflammatory factors (e.g., TNF-α, interleukin (IL)-6, IL-1β), reactive oxygen species (ROS), proteolytic enzymes, and other active molecules to actively dictate an early cascade of immune responses. On the other hand, by secreting anti-inflammatory factors (e.g., IL-10), monocytes can also actively engage in the inflammation suppression process which is essential for maintaining tissue homeostasis (25, 26).

3.4. Function of DCs in inflammation

As discussed in previous studies, the immune system can be efficiently activated by anatomical, immunological, genetic, and environmental cues in the early stages of life. In addition to conventional DCs which arise from hematopoietic progenitor cells in the BM, a heterogeneous sub-population called inflammatory DCs can be derived from monocytes which are recruited to the local sites where inflammation occurs. It has also been observed that the nuclear factor kappa B (NF-κB) pathway engaged in TLR-4 signaling is well preserved in neonatal monocyte-derived DCs (MoDCs), which are in charge of maintaining the generation of pro-inflammatory factors (e.g., TNF-α, IL-6, and IL-8). This helps scholars to better understand the molecular mechanisms underlying the diminished ability of circulating MoDCs to generate inflammatory cytokines such as TNF-α or IL-1β, contributing to the vulnerability of newborns to bacterial sepsis (27).

4. ROLE OF MYELOID HO-1 IN THE PATHOLOGICAL PROCESS OF INFLAMMATION

Inflammation is a dynamic process engaging diverse cellular and subcellular elements that undergo a complex interplay. Those elements operate in a collaborative fashion to defend the host against deleterious stimulation (28). Current views state that the inflammation process can involve both the innate immune system and adaptive immune system for orchestrated regulation of immunity. Essentially, modulating the myeloid HO-1 may cross-regulate these two processes.

4.1. Role of myeloid HO-1 effects on NKT and NK cells

Natural-killer-T (NKT) cells, harboring cytotoxicity and cytokine-producing functions, are significant components of the innate immune system. They can quickly respond to virally infected cells and tumor cells and can generate diverse cytokines correspondingly. In addition to their long-term acknowledged effector lymphocyte function, recent discoveries underscore their regulatory role in communicating with other types of lymphocytes as well. For instance, antigen-presenting DCs can be activated by NKTs (29), and T cells can be induced to form differential Th1 cells after direct interaction with NKTs (30). Genetically, deletion of HO-1 in multi-drug resistance protein 2 (Mdr2) knockout mice leads to a more severe inflammation phenotype compared with Mdr2-only knockout littermates. This exacerbation could be explained by the corresponding elevated frequencies of T cells, NKT cells, and mature dendritic cells (DCs) compared to Mdr2-only knockout littermates (31). NK cells can interfere with the delicate balance between the regulatory and effector input part

of the immune response through eliminating regulatory T cells (T-reg) (32). Induced HO-1 expression in mice reveals a severe suppression of T cell and NK-cell-mediated spleen cell toxicity (32).

4.2. Role of myeloid HO-1 effects on T cells

T-lymphocytes are essential players and a core component for adaptive immunity, governing the host's immune response toward different pathogens (33). T-lymphocytes are mainly divided into two subpopulations based on the marker expression pattern on their cell surface, namely, CD4+ and CD8+. In addition to carrying out multiple layers of functions in immunity, CD4+ helper T cells promote activation of cells engaged in the innate immune system, B-lymphocytes, and other nonimmune cell types. On the other hand, they contribute to dampening the active immune response based on their regulatory property. CD8+ cytotoxic T cells can specifically destroy their target (i.e., cancer cells, infected cells, or damaged cells from other sources) through releasing their cytotoxins to induce apoptosis. Releasing soluble factors and cytokines is an important means for T cells to communicate with other cells as well as defining the local immune environment. The distinct patterns of released cytokines could be proinflammatory or anti-inflammatory. Additionally, T cells release soluble factors that can activate and recruit immune cells or modulate their functions (34). Several studies have indicated that myeloid-derived HO-1 affects the function and development of human and murine CD4+ and CD8+ regulatory T cells (T-reg). Myeloid dendritic cells expressing HO-1 have been shown to potentially drive the enhancement of Foxp3 regulatory T cells through unknown mechanisms (35). However, the contribution of HO-1 activity in the inhibition of inflammatory molecules produced by T cells has not yet been identified. Findings support the notion that myeloid HO-1 expression can actively impact many aspects of T cell biology potentially through a dissected cell-cell communication network. Brandsma (36) reported that HO-1 induction, particularly in lung alveolar macrophages, was correlated with the inhibition of smoking-induced B-cell infiltrates in lung. This phenotype was accompanied with elevated CD4+CD25+ regulatory T cells in lung (36). These studies provided strong evidence about the myeloid HO-1 function in regulating inflammation, and further enabled scholars to infer that manipulation of myeloid HO-1 level could serve as a novel means to regulate immune cell (i.e., T-regs) responses toward an anti-inflammation outcome. Moreover, our previous findings revealed that the application of the precursor of heme anabolism, 5-aminolevulinic acid (5-ALA), together with the byproduct of heme catabolism, ferrous iron, interestingly upregulated HO-1 expression in myeloid cells and led to T cell proliferation repression in a murine cardiac allograft model (37). However, in this model, regulatory T cells and myeloid cells received significant expansion, leading to alleviation of the organ allotransplantation rejection phenotype and eventually to successful allograft acceptance. Collectively, all these findings support the idea that myeloid-derived HO-1 plays a critical role in immune tolerance, and manipulation of its expression level adds a novel layer of regulation beneficial for clinical treatment of inflammation.

4.3. Role of myeloid HO-1 effects on B cells

B cells, a critical component of adaptive immunity, carry out the humoral immune response through secreting antibody molecules. Furthermore, B cells can also release cytokines and actively engage in regulating the function of other immune cells (e.g., T cells and DCs) to realize its regulatory role in immunity (38). Kapturczak *et al.* discovered that HO-1 gene deletion in mice led to diminishing the number of $B220^{+}$ cells in the lymph nodes (39). In these animals, levels of serum immunoglobulin M (IgM) were dramatically increased and irregular immunoglobulin profiling was demonstrated (40). These data strongly support the concept that HO-1 gene expression can impact B cell functions (41). We can infer that myeloid-derived HO-1 might contribute to the above-described phenotype, and that this enzyme is vital for B cell inflammation.

4.4. Molecular mechanisms of myeloid HO-1 gene regulation

HO-1 gene expression primarily responds to numerous biological stress stimuli including oxidative stresses and their inductions, which are regulated through diverse signaling pathways primarily at the transcriptional level (42). Among the identified HO-1 gene regulatory DNA motifs in mouse models, stress-responsive elements or antioxidant response elements (ARE) have been shown to be a dominant cis-regulatory element which also exists in the human HO-1 gene promoter region. Transcriptional regulation of the HO-1 gene can be carried out through dynamic interactions between transcriptional activators or repressors and the regulatory DNA motifs. Transcriptional activators such as nuclear factor erythroid 2-related factor-2 (Nrf2) or transcriptional repressors (e.g., Bach1) can competitively occupy the ARE domain of the HO-1 gene promoter, which can lead to modulation of gene expression. Furthermore, evidence supports the notion that inactivation of Bach1 was indeed a prerequisite for HO-1 gene induction. To add an extra regulatory layer to this dynamic process, it was shown that HO-1 gene expression can also be regulated by its substrate heme, which is able to form a complex with the transcriptional repressor Bach1 to prevent its binding with the HO-1 gene enhancer and promote its nuclear export as well. Previous results, obtained by the authors, showed that application of

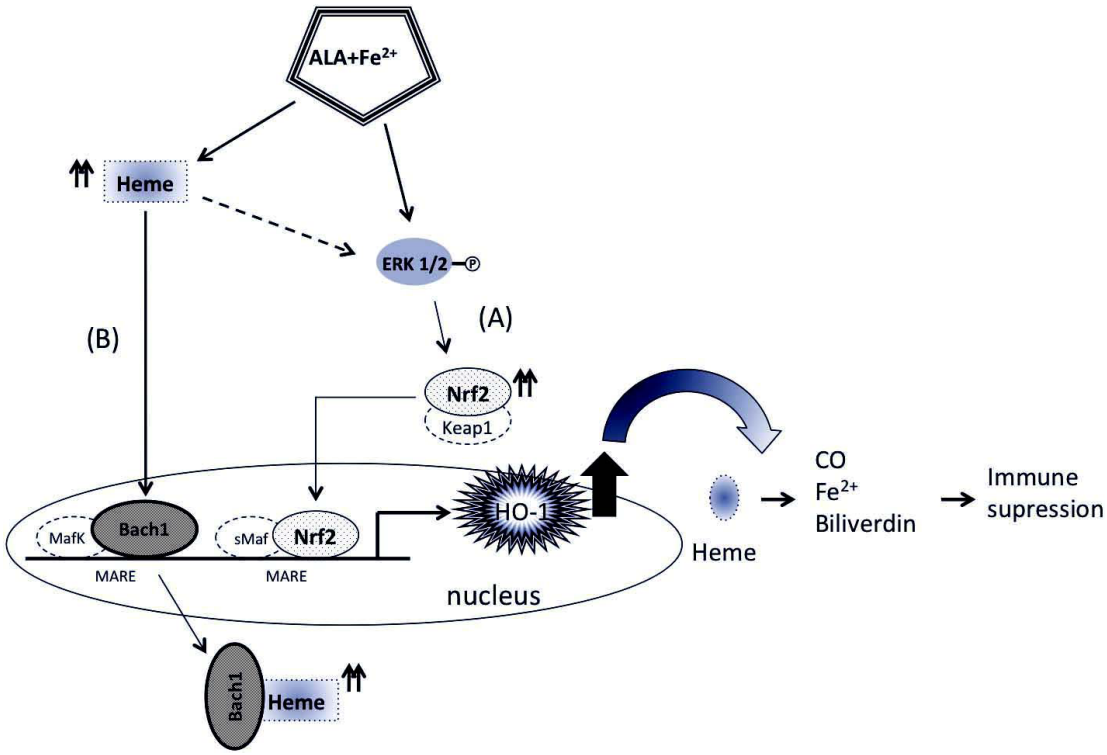

Figure 2. A model of HO-1 induction based on our observations. 5-ALA metabolism induced HO-1 expression through (A) and (B) pathways in myeloid cells (RAW264.7.). Treatment with 5-ALA combined with Fe^{2+} induces the phosphorylation of ERK and p38 MAPK. These activated MAPKs lead to HO-1 expression through their effects on post-transcriptional factors, such as Nrf2. On the other hand, exposure to 5-ALA/Fe^{2+} increases the intracellular levels of heme. Under conditions with a higher concentration of heme, the HO-1 repressor, Bach1, is inactivated by direct binding of heme to Bach1, which allows for increased expression of HO-1. The induction of HO-1 via at least two pathways leads to reduced levels of inflammatory cytokines.

the precursor of heme anabolism (5-ALA) together with the byproduct of heme catabolism (ferrous iron) in the macrophage cell line RAW264.7. up-regulated the HO-1 gene expression for an anti-inflammation effect, which could be suppressed by mitogen-activated protein kinase (MAPK) pathway inhibitors (43). NFE2L2 (Nrf2) activator, and intracellular increment at the heme level, were observed in the treated RAW264.7. cells, suggesting a Bach1 inactivation mechanism to facilitate HO-1 gene upregulation, as shown in Figure 2) (43).

A number of other proximal promoter components, such as upstream stimulatory factor, basic helix loop helix proteins, NF-κB, signal transducer and activator of transcription 3 (STAT3), activator protein-2, hypoxia-inducible factor (HIF)-1, activating transcription factor 2 (ATF2), and heat shock factor 1 (HSF1) are all among the growing inventory list contributing to HO-1 gene regulation. The multiplicity of this complex gene fine-tuning network establishes a platform for developing pharmaceutical intervention methods targeting HO-1 gene production for therapeutic application. Pharmaceutical activation or inhibition of some promoter elements can induce expression of HO-1 proteins that efficiently rescue cells from inflammatory stress (44).

MAPK signaling is well acknowledged for its significant role to elicit a variety of biological changes in response to extracellular cues. Our lab and other groups revealed that MAPK signaling cascade is a crucial player involved in Nrf2 transcription factor activation, which is required for inducing HO-1 expression to exert its anti-oxidative stress function (43, 45-48). In addition, other signaling molecules including tyrosine kinase, protein kinase C, NF-κB, and phosphatidylinositol 3-kinase/Aktare are all included in the critical list for HO-1 expression regulation (see Figure 3) (49-51).

4.5. Protective role of myeloid HO-1 in inflammation diseases

In mammals, HO-1, as a stress-responsive enzyme, catabolizes heme into CO, free iron, and biliverdin in the presence of molecular oxygen and electron source for nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome p450 reductase. The generated biliverdin is further reduced to bilirubin by biliverdin reductase. Both biliverdin and bilirubin showed direct anti-oxidative properties by eliminating excessive ROS whose elevated level is believed to significantly contribute to chronic inflammation and pathogenesis (52-

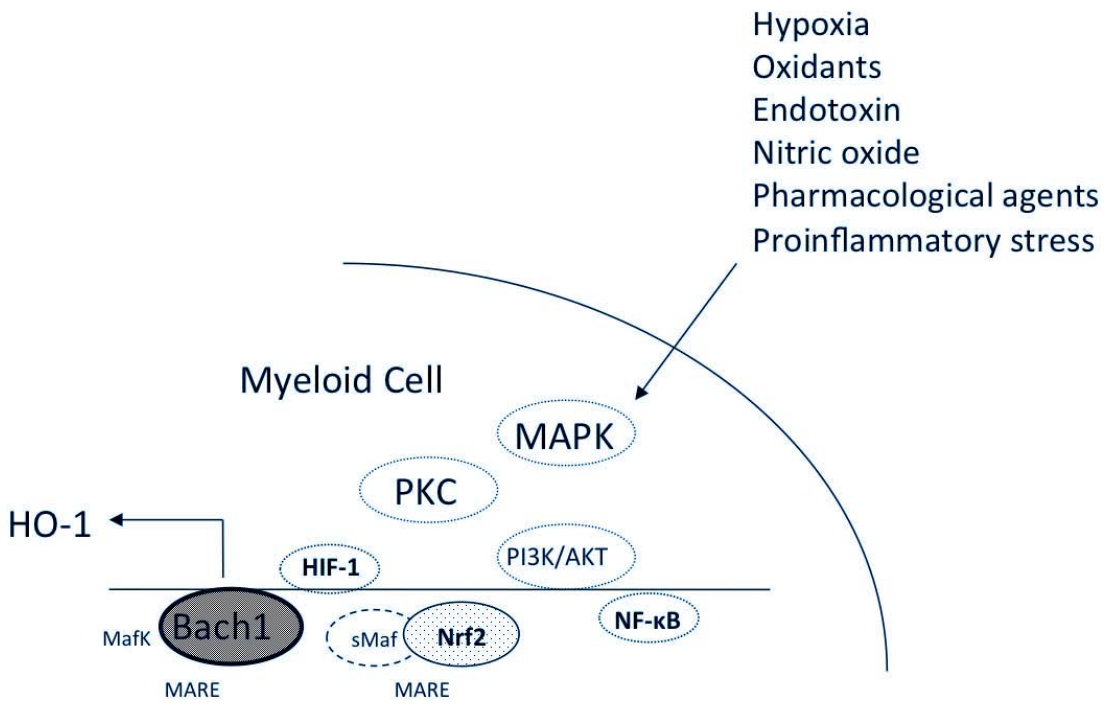

Figure 3. A diagram of the HO-1 signaling pathways. External and internal stimulus factors, such as hypoxia, oxidants, endotoxin, nitric oxide, pharmacological agents, or proinflammatory stress, up-regulate HO-1 expression via several kinase cascades and transcription factors.

54). In addition, CO, through directly regulating diverse transcription regulation programs and inflammation-associated molecules, significantly conveys the beneficial effect of HO-1 protein in combating inflammation (55). Recently, it was discovered that HO-1's anti-inflammation and immunomodulation function can be tightly linked to myeloid or endothelial origin-derived expression (56). In myeloid cells, HO-1 is believed to induce downregulation of tumor necrosis factor (TNF-α) and upregulation of IL10; these HO-1 mediated events at the molecular level are further associated with cell differencing commitment to tolerogenic antigen presenting cells, which are promising mediators for treating inflammatory diseases. Importantly, in multiple elegantly established *in vivo* organ-system inflammatory models, evidence indicated that HO-1 could positively execute its protective potential for homeostasis recovery through modulation of tissue responses to injury, as shown in Table 1.

4.6. Myeloid HO-1 bridges a crosstalk between autophagy, apoptosis, oxidative stress, and inflammation

A growing body of evidence supports the concept that autophagy, an adaptive cell catabolic program that eliminates harmful intracellular components, can play diverse roles in response to ROS-triggered oxidative stress signals. Through preserving mitochondrial integrity and degrading nonfunctional proteins, autophagy provides a survival mechanism under stress which is also significant for modulating the inflammation process and immune functions (57). HO-1 or exogenous application of its reaction product CO, has been shown to confer a cytoprotective role through the modulation of apoptotic-autophagy and/or inflammatory signaling in models of inflammatory stress, as depicted in Figure 4 (58-60). Indeed, the HO-1/CO axis has also been shown to protect stress-insulted cells from incurred apoptosis, therefore shifting cell fate toward survival.

Using pharmacological intervention or genetic manipulation methods, *in vivo* evidence highlights the importance of HO-1 and its end products in affording protective effect in tissue injury models through induction of autophagy (61). Furthermore, in macrophages stimulated by lipopolysaccharide (LPS), HO-1 was shown to mediate autophagy which further leads to anti-inflammation and cytokine production repression phenotype (60-63). A previous study also suggested that HO-1 induction by 5-ALA together with ferrous iron (SFC) inhibited hypoxia-caused cellular injury in cardiomyocytes through autophagy (45).

5. COMPOUNDS AS MYELOID HO-1 EXPRESSION INDUCER

Various inducers for HO-1 expression are known to have potent cytoprotective properties, such

Table 1. Protective role of HO-1 expression in inflammation diseases

Organ	Injury/Disease Model	Mechanism	Reference
Brain	• HIV infection • Diabetes • Parkinson's disease • Hypoxia-induced brain injury • Lipopolysaccharide-induced acute inflammation	• Endogenous antioxidant and immune modulatory • NF-κB p65 inhibition • Nrf2 pathway • PI3K/Akt/Nrf-2 signal pathways • Oxidative reaction	(66) (67) (68) (69) (70)
Eyes	• Endotoxin-induced uveitis	• Increased cytokine production	(71)
Skin	• UVB irradiation • TPA-induced inflammation	• Nrf2 pathway • IL-1 beta and TNF-alpha	(53, 72) (73)
Lung	• LPS-induced inflammation • Acute pulmonary inflammation	• p38MAPK-dependent • Inhibiting the release of segmented PMNs from the BM	(74) (75)
Heart	• Cardiac dysfunction	• Inhibition of oxidative stress, inflammation, and apoptosis	(76)
Gastrointestinal tract	• Inflammatory diseases	• Anti-inflammatory, anti-proliferative, antioxidant, and anti-apoptotic	(77)
Liver	• Liver fibrosis • Ischemia and reperfusion	• Nrf2/ARE signaling pathway • Nrf-2/Akt-p70S6k signaling pathway • Notch1/Hes1/Stat3 signaling	(78) (79) (80)
Bone marrow	• Transplantation	• Reduced T-cell activation *ex vivo*	(81)
Kidney	• Ischemia/reperfusion • Polycystic kidney disease	• Produce the potent cellular antioxidant bilirubin • Reduced antioxidant enzyme	(52, 82) (83, 84)

GI: Gastrointestinal, BM: Bone marrow,

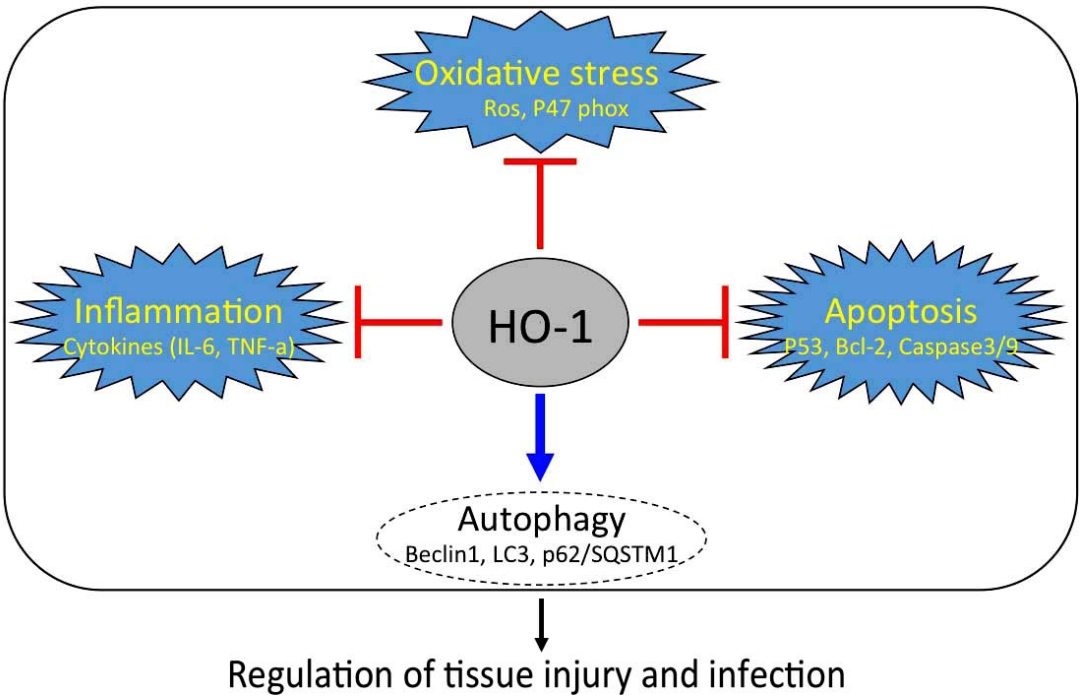

Figure 4. Crosstalk between autophagy, apoptosis, oxidative stress and inflammation by HO-1 overexpression.

as hemin, epigallocatechin-3-gallate, rosiglitazone, gastrodin, methotrexate (MTX), and curcumin. This review details the effects of two compounds, 5-ALA and dihydroquercetin (DHQ), which have been recently studied by our research group.

5.1. Aminolevulinic acid (5-ALA)

5-ALA, a naturally occurring important metabolic intermediate, is a necessary precursor of heme. A previous study discovered that in a renal

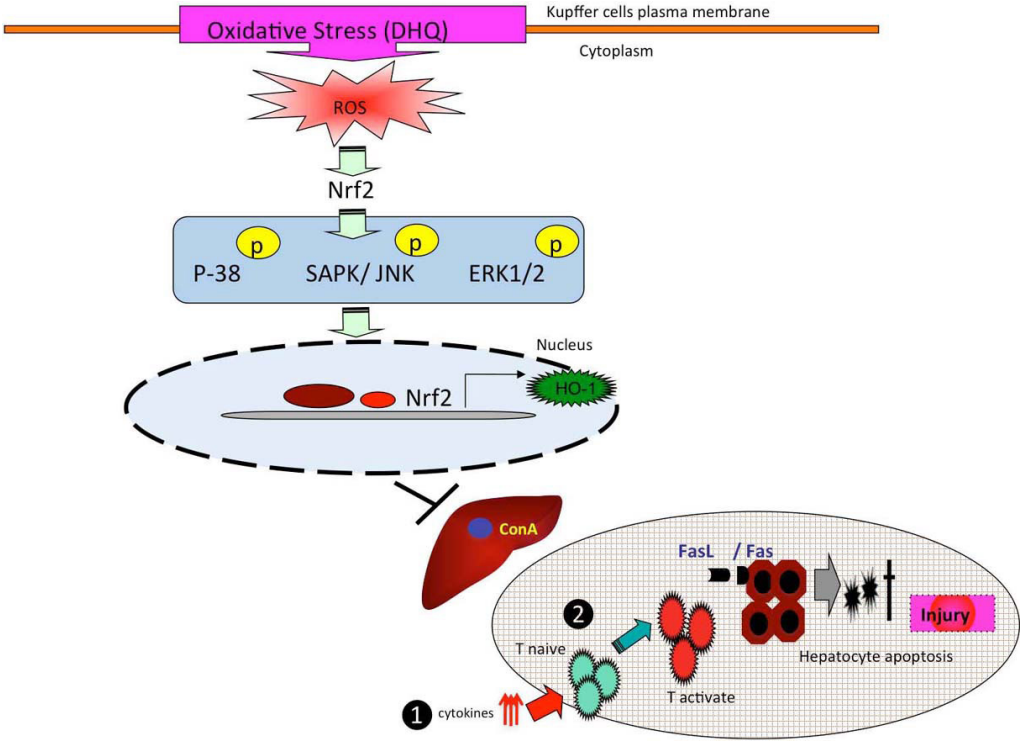

Figure 5. Dihydroquercetin (DHQ) ameliorated concanavalin A-induced experimental fulminant hepatitis in mice and enhanced HO-1 expression through the MAPK/Nrf2 antioxidant pathway in RAW cells.

ischemia reperfusion injury (IRI) model, a 5-ALA/SFC combination application before the surgery dramatically attenuated the severity of the IRI with significantly alleviated tubular damage and apoptosis inhibition. Furthermore, the detected amount of renal thiobarbituric acid-reactive substance was considerably lower in the 5-ALA/SFC combination application group, which could be attributed to the elevated HO-1 regulation followed by the corresponding high production of the end product CO in initiating the protective effect through downregulating TNF-α and interferon gamma (IFN-γ) in the renal parenchymal tissue. Interestingly, macrophage infiltration was found to be diminished in the 5-ALA/SFC combination-treated renal group, suggesting a potential mechanism of 5-ALA/SFC—HO-1—CO axis-induced immunomodulatory effect in protecting kidney from detrimental stimuli, IRI in this case (64).

5.2. Dihydroquercetin (DHQ)

DHQ, a natural compound found in plants, has been long perceived as a potent anti-oxidant agent that holds promise for fighting a variety of diseases, including liver disease. Using our established *in vivo* experimental platform (65), we were able to show that DHQ application efficiently protected mouse livers from concanavalin A (ConA)-induced damage, evidenced by reduced liver function impairment index serum alanine transaminase (ALT) and aspartate transaminase (AST) levels, improved histopathological outcome, and boostered animal survival rate. We further found that various proinflammatory cytokine mRNA levels underwent remarkable reduction in the liver tissues from DHQ-treated animals, suggesting involvement of an immunomodulation process as a potential mechanism explaining DHQ's beneficial effect in liver protection. Based on the belief that liver macrophages/ Kupffer cells carry essential distinct functions in response to oxidative stress and inflammatory stimuli for governing liver homeostasis and pathogenesis, the authors were prompted to explore their response by applying ConA to a mouse RAW264 macrophage cell line. The results showed that DHQ treatment can obviously block the transcription level of IFN-γ and TNF-α, and further diminish their secretion in culture. To dissect the potential underlying mechanisms, the authors focused on HO-1 and demonstrated that its expression was markedly raised in a dose- and time-dependent fashion by DHQ, probably through the signaling from the upregulated transcriptional activation factor Nrf2. Furthermore, DHQ stimulated phosphorylation of three MAPK family members, and application of the inhibitors of MEK/ERK (PD98059), p38 (SB203580), and JNK (SP600125) blocked DHQ-mediated HO-1 upregulation (65) (see Figure 5).

6. SUMMARY AND CONCLUSION

In summary, the presence of myeloid HO-1 serves a protective role at the site of tissue

injury. Given this positive role, perhaps laboratory approaches, in order to increase myeloid HO-1 levels for anti-inflammation therapeutic purposes, should be considered for translation from benchtop to clinical applications. However, further understanding the mechanisms of myeloid HO-1 in the pathogenesis of inflammation diseases may be required to safely create and efficiently design treatments for use in clinical practice.

7. ACKNOWLEDGMENTS

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