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Review article

Heme oxygenase-1 as a potential therapeutic target in rheumatic diseases

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ABSTRACT

Background: Heme oxygenase-1 (HO-1), a cellular stress protein, serves a vital metabolic function as the rate-limiting enzyme in the degradation of heme to generate carbon monoxide (CO), iron, and biliverdin (BR). HO-1 may function as one of the most momentous factors of cell adaptation to oxidase stress, as well as a regulator of inflammatory signaling programs through the generation of its biologically active end products. Intensive investigation is now focusing on the potential function of HO-1 in inflammatory disorders, among which rheumatic diseases are one of the principal issues.

Methods: "Heme oxygenase-1", "rheumatic diseases"; "lupus", "rheumatic arthritis", "osteoarthritis" and "oxidative stress" were used as key words for searching in Pubmed and Google scholar database.

Results: Collected information from the related articles revealed the important role of pathogenesis and therapeutic potential of HO-1 in rheumatic diseases.

Conclusions and discussions

HO-1 has potential as a target for the treatment of rheumatic diseases due to its characteristic anti-inflammatory and anti-oxidative role. However, it is essential to monitor the HO-1 expression during particular stage of the disorders, and levels of HO-1 in different tissues and organs should be further confirmed in order to correlate it with clinical symptoms and other hallmarks of rheumatic diseases.

1. Introduction

The heme oxygenase (HO) is a stress-responsive enzyme system that can catabolizes free heme into biliverdin, carbon monoxide and iron [1]. Free heme is essential for controlling the expression of numerous proteins such as HO-1, nitric oxide synthase, cytochromes and so on. It also regulates proliferation and differentiation of a variety of cells [2]. Besides its physiological importance, heme has a potent oxidative capacity in oxidizing lipids and proteins, and damaging DNA [3]. Excess of heme may be pathogenic because heme catalyzes the formation of reactive oxygen species (ROS), resulting in oxidative stress and subsequent cellular or tissue damage. Furthermore, it is known that chronic oxidative stress promotes inflammatory responses in multifarious immune-mediated diseases and contributes to pathogenesis. Thus, HO enzymes possess a crucial metabolic function by heme bioavailability regulation and turnover in cells or tissues during oxidative stress.

HO activity is represented by 3 separate isozymes: an inducible isoform HO-1, and two constitutively expressed isoforms HO-2 and HO-3. The inducible isoform HO-1, exhibited low basal expression levels in most cells and tissue, and expressed highest in the spleen, the site of erythorocyte turnover [4]. HO-1 is undetectable under basal conditions but highly inducible under conditions of stress or inflammation [5]. HO-2, is also an important component of cells that participates in the regulation of various physiological processes [6]. In contrast, the so-called HO-3 form, studies of which are still limited, was proved to be a processed pseudogene derived from an HO-2 transcript [7].

Rheumatic diseases are a range of more than 100 chronic and disabling illnesses seriously affecting people's life. It is featured by inflammation infiltration and loss of function in one or more regions of musculoskeletal system, such as cartilage, joints, muscles, bones, tendons, ligaments, even internal organs [8,9]. Most rheumatic diseases exhibit autoimmune or inflammatory disorders. For instance, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), osteoarthritis are typical rheumatic diseases accompanying with disorders of immune

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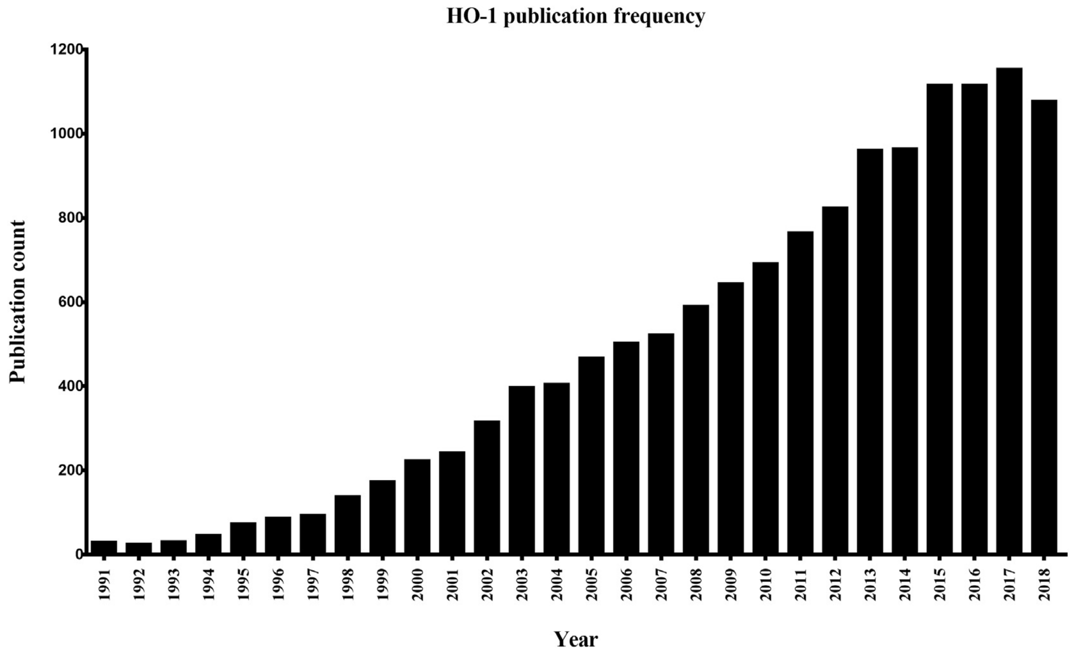

Fig. 1. Publication count of articles on HO-1 in the Pubmed database. Publications per year when searching "HO-1" in Pubmed database. Search term: [(Heme oxygenase 1 OR Haem oxygenase 1) OR (HO-1 OR HMOX1)].

system. Although rheumatic diseases are complex and considerably different in etiology, clinical manifestations and therapies, there is resemblance in pathogenic mechanisms involved. In the last decade, accumulating evidence supported contribution of oxidative stress to the symptoms and progression of inflammatory diseases and common rheumatic diseases [10]. Notably, HO-1 exhibits critical immune-modulatory functions in macrophages, which play essential roles in immune system especially in rheumatic diseases [1]. Some therapies targeting HO-1 in experimental models have been confirmed beneficial for attenuating the severity of these rheumatic diseases. It suggests that the cytoprotective effect of HO-1 against oxidative stress and inflammation has the potential to be a burgeoning therapeutic strategy for a series of immune-related rheumatic diseases.

Based on the multiple biological characteristics of HO-1, interest in it continues to grow rapidly (Fig. 1). Nowadays, there have been plenty of publications about the essential role and therapeutic potential of HO-1 in diversified disorders including tumor, vascular diseases, diabetes and obesity. Despite the growing interest in the protective role for HO-1 in rheumatic disease (Fig. 2), the definite function of HO-1 in immunological modulation is only scarcely understood. This review highlights the significant impact of HO-1 in rheumatic diseases and provides a brief overview of rheumatic diseases therapies targeting HO-1 based on the informed researches.

2. Methods

2.1. Data sources and searches

Pubmed and Google scholar, as the main two databases, were searched regarding "heme oxygenase-1, rheumatic diseases, lupus, rheumatic arthritis osteoarthritis and oxidative stress" as key words. The articles published from 1991 to 2018 have been enrolled in current review. A board and comprehensive strategy was chosen to include the range of content associated with the role of HO-1 in rheumatic diseases. Accordingly, 81 papers were included in the article.

2.2. Search strategy and article selection

The search for articles on HO-1 showed 9418 articles. The articles were further refined by searching two key words including "HO-1 and rheumatic diseases", after which 55 articles remained. The review articles and research and short papers regarding the function of HO-1 in other diseases were excluding from the study. Then, use HO-1 and disease name for searching in databases to evaluate the function of HO-1 and the strategy of HO-1 as therapeutic target in specific disease.

The articles were divided into two categories: 1) the first category include animal studies on the models associated with rheumatic diseases. In the animal models, expression of HO-1 in different cells and tissues and the progression of the diseases through targeting HO-1 were measured. 2) The second category included clinical studies in human consisting rheumatic diseases. In the clinical trials, only the level of HO-

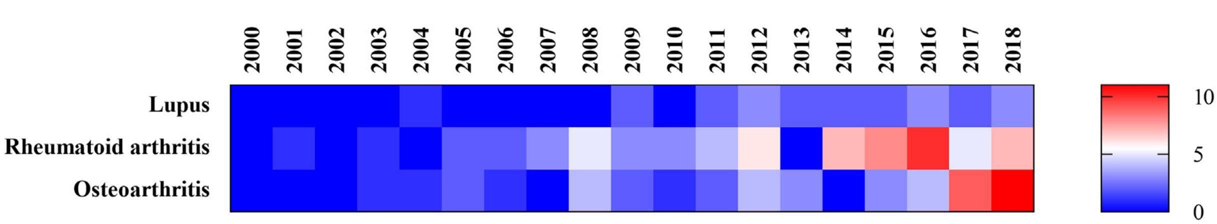

Fig. 2. Heat Map for publication count of articles on HO-1 and different rheumatic diseases in the Pubmed database. Publications per year when searching "HO-1 and different rheumatic diseases" in Pubmed database. Search term: [(Heme oxygenase 1 OR Haem oxygenase 1) OR (HO-1 OR HMOX1)] AND (Disease Name[MeSH] OR Disease Name[tiab]).

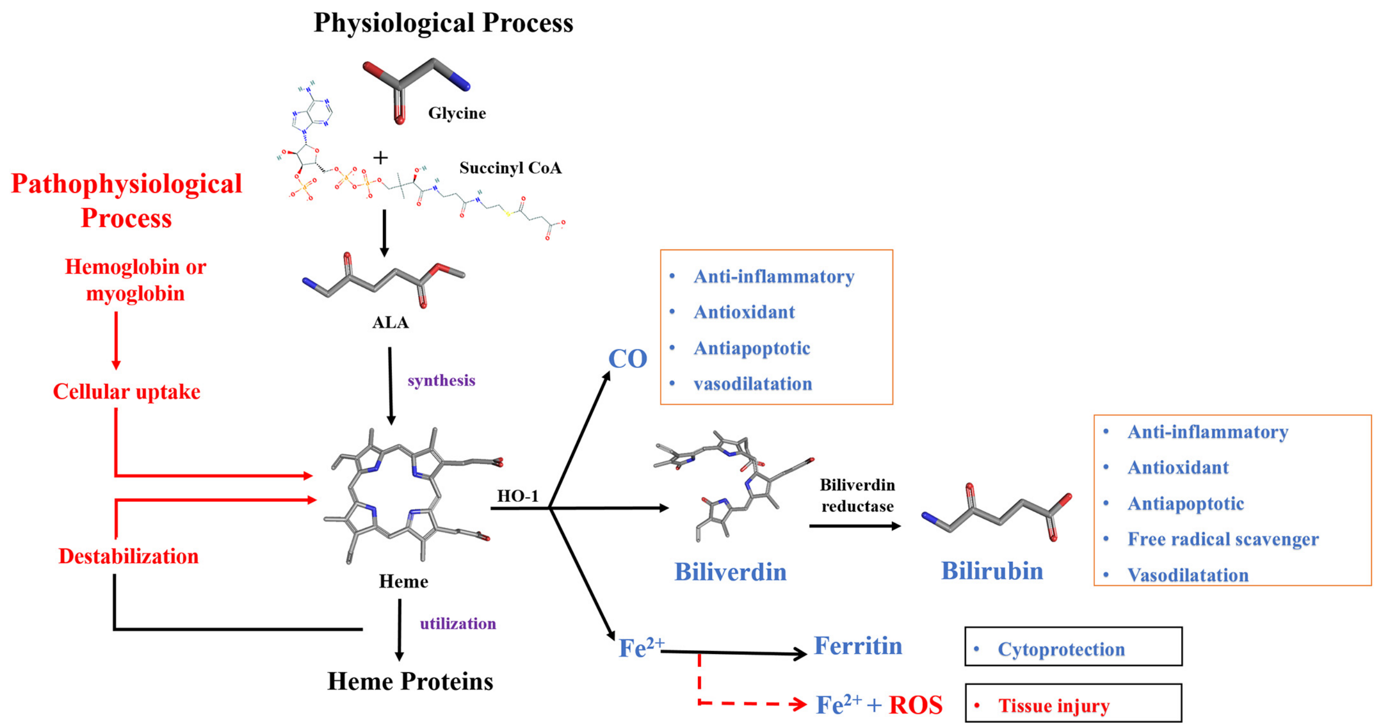

Fig. 3. Synthesis of heme under different conditions and biological function of HO-1. HO-1 catabolizes the degradation of heme into CO, biliverdin and Fe^{2+}. The products of HO-1 enzymatic reaction play essential role in numerous biological process. Succinyl CoA, succinyl coenzyme A; ALA, 5-aminolevulinic acid; CO, carbon monoxide; HO-1, heme oxygenase-1.

1 expression in cells and tissues of patients were mentioned.

3. Heme and heme oxygenase-1 (HO-1)

3.1. Biological function of heme and HO-1

Heme is an important molecular composed of iron with protoporphyrin IX [11]. It plays an essential role in varieties of biological reactions including oxygen metabolism, stress response, protein synthesis and cell differentiation in aerobic cells [12]. Heme is a prosthetic group of numerous hemoproteins and myoglobins, which are essential in synthesis of regulatory and signaling molecules such as guanylate cyclase and nitric oxide synthase. Under physiological conditions, the first step occurring in mitochondria is the condensation of glycine and succinyl coenzyme A (CoA) to form 5-aminolevulinic acid (ALA), which is catalyzed by ALA synthase. Finally, ALA is converted into heme in the presence of a series of essential enzymes. However, in numerous pathophysiological processes, hemoproteins will be took in by cells which lead to production of free heme (Fig. 3). Free heme is a ubiquitous cytotoxic molecule catalyzing the production free radicals and involved in the pathogenesis of many inflammation associated diseases.

There are a specific set of heme degrading enzymes in animal cells known as heme oxygenases, which are encoded by Hmox gene and rate-limited. Heme oxygenase-1 (HO-1) is one of the three different isoforms (HO-1, HO-2 and HO-3) which can be expressed on different conditions and in different tissues. HO-1 is expressed almost in every cell of the organism and is upregulated as reply to various stimuli including inflammation, vascular and immune injury and so on in mammalian tissues [13–15]. Importantly, HO-1 is a 32-kDa inducible protein that can degrading heme into carbon monoxide (CO), equimolar amounts of Fe^{2+} and biliverdin, which exhibit corresponding properties [16] (Fig. 3). Among those, CO has widely therapeutic potential in anti-inflammatory, neuroprotective and mitochondrial action [17]. Fe^{2+} induces the expression of ferritin heavy chain (FtH) which contributes to the virtual anti-oxidative effects of HO-1 [18]. However, if the ferritin synthesis is not sufficient, the surplus free iron will react with ROS (the Fenton reaction) and lead to generation of the highly toxic hydroxyl radical, which results in inflammatory response and tissue damage such as renal fibrosis and paw edema. Additionally, the biliverdin can be converted into cytoprotective antioxidant bilirubin by biliverdin reductase, both of which are regarded as ROS scavengers have underlying anti-inflammatory and antioxidant competence [19]. In general, the products of heme catabolism can solely or in combination contribute to the antioxidant and cytoprotective effects of HO-1. Better yet, the degradation of heme prevents it from accelerating oxidation and should be salutary as such.

3.2. Regulation of HO-1 gene expression

Redox-dependent Keap1/Nrf2 and Bach1 system is closely linked to the regulation of HO-1 expression (Fig. 4). The Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1-nuclear factor erythroid 2-related factor 2 (Keap-1-Nrf2) pathway is an important mechanism executing protective function of HO-1 against oxidative stress [20]. Under physiological conditions, Nrf2 is restrained in the cytoplasm by Keap1, which facilitates the ubiquitination of Nrf2 by the Cullin 3-based E3 ubiquitin ligase complex [21]. Afterwards, in response to oxidative stress, the harmful molecules can active Keap1 sulfhydryl groups to release Nrf2 and make it translocate into nucleus. Afterwards, Nrf2 binds to the Antioxidant Response Elements (ARE) in the promoter region of an extensive range of target genes coding antioxidant and detoxifying enzymes, such as hemeoxygenase 1 (*HMOX1*), NAD(P)H quinone oxidoreductase 1 (*NQO1*), glutamate-cysteine ligase (GCL) and glutathione S transferases (GSTs), which execute anti-oxidative function in cells [22–24].

In addition, the BTB and CNC homologue1 (Bach1) transcription factor competes with Nrf2 binding sites in the HO-1 promoter region resulting in repression of HO-1 expression [25]. Only during stress response conditions, Bach1 is inactivated and changes its configuration

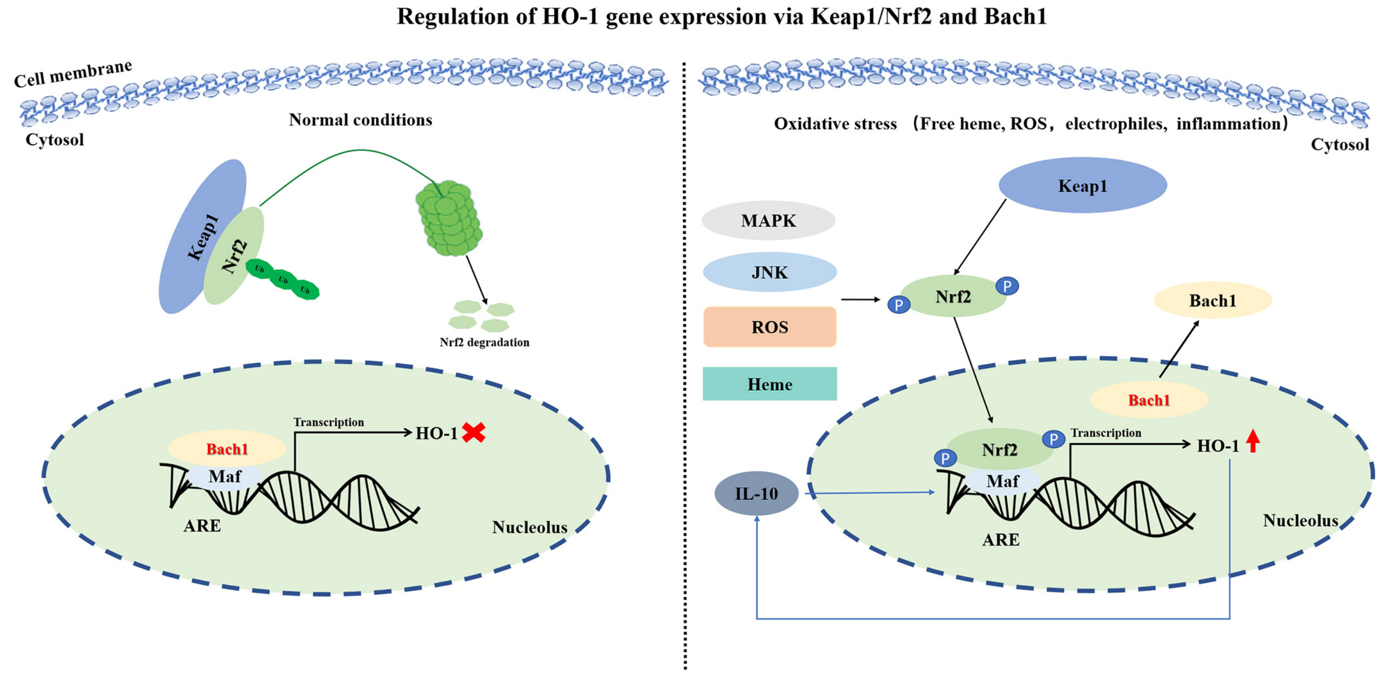

Fig. 4. Redox-dependent Keap1/Nrf2 and Bach1 system regulate HO-1 expression. Under the normal condition, Nrf2 remains in the cytoplasm as bound to Keap1. Constantly ubiquitinated Nrf2 is targeting for degradation in the proteasome. Bach1 with small Mafs proteins bind to Antioxidant Response Elements (ARE) in the promoter region of HO-1. In response to cell oxidative stress caused by pro-oxidant molecules or inflammation, Bach1 is inactivated and dissociates from the HO-1 promoter and Nrf2 is released by Keap1 and translocates into nucleus. Different kinases including MAPK and JNK can catalyse the phosphorylation of Nrf2, allowing it traslocation into nucleus. Nrf2 and Maf heterodimers binding to ARE induce the activation of Hmox1 transcription.

and dissociates from the HO-1 promoter, then Nrf2 can bind to AREs and activate transcription of HO-1 [25]. Certainly, in regard to the regulation effect of HO-1 expression, it is certified that Keap1/Nrf2 and Bach1 system are driven by pro-oxidant and pro-inflammatory molecules such as pathogen-associated molecular pattern (PAMPs) and damage-associated molecular pattern (DAMPs) including heme and ROS. They can activate the mitogen-activated protein kinases (MAPK) and c-Jun N-terminal kinases (JNK) pathways and therefore catalyse the phosphorylation of Nrf2, allowing it translocation into nucleus. Beyond that, not only the pro-inflammatory stimuli but also the anti-inflammatory molecules including IL-10 can induce the transcription of *Hmox1* gene. Correspondingly, HO-1 expression also promotes IL-10 production [26].

Consistent with these notions, it is confirmed that Nrf2-deficient female mice display a shortened lifespan and develop sever lupus-like autoimmune nephritis and the deficient of Nrf2 could confer a risk for developing kidney malfunction in SLE-affected individuals [27,28]. In conclusion, both Nrf2 and Bach1 are crucial for the induction of HO-1 and might provide greater chance for organisms to adapt to the oxidative stress conditions.

Interestingly, emerging researches suggest that microRNAs (miRNAs) play a critical role in the modulation of HO-1 expression. MiRNAs are small noncoding RNA molecules that are correlated with gene silencing and posttranscriptional regulation of gene expression. A number of miRNAs including miR-377, miR-217, miR-378, miR-24, miR-204/miR-211, miR-155 were identified in translational regulation of HO-1 [29–34]. There are also miRNAs indirectly modulating the HO-1 upstream regulatory factors, such as Bach1, Nrf2 and keap1. For instance, miR-155 can downregulate expression of Bach1 and therefore promote the HO-1 expression [35]. MiR-200a can promote Nrf2 activation by targeting keap1 [36]. Additionally, miR-101 can target the Cullin3, E3 ubiquitin ligase and stabilize Nrf2, resulting in activation of HO-1 expression [37]. It is intricate that HO-1 can also regulate miRNAs, indicating that a miRNA dependent network also plays a vital role in the HO-1 regulation and function. The particular interaction between HO-1 and miRNAs may prompt neoteric pathway and conceivable therapeutic targets in different clinical disorders including rheumatic diseases.

4. Involvement of HO-1 in rheumatic diseases

4.1. Systemic lupus erythematosus

SLE is a systemic autoimmune disease characterized by increased production of nuclear auto-antigens, elevated secretion of proinflammatory cytokines, imbalanced proportion of immune cells including lymphocytes and leukocytes and severe tissue and organ damage [38]. Not only genetic factors but also many environmental agents caused by oxidative stress such as infections, Ultraviolet light (UV) can attribute to SLE [39]. Moreover, all these environmental factors lead to abnormal redox reaction in organism which will result in noxious cytokines effect, abnormal lymphocytes behavior, decreased activity of some enzymes and increased cell death. There are accumulating evidences that support the important function of HO-1 in the immunoregulation of SLE. Due to this, interest in HO-1 and relationship between HO-1 and SLE has been increased rapidly.

Previous researches have confirmed that the levels of HO-1 in kidney were decreased in patients with proliferative lupus nephritis [40]. Additionally, HO-1 levels in monocytes are significantly reduced in patients with SLE compared with healthy controls, and no differences are observed in other cell types, such as DCs or $CD4^+$T cells, suggesting that an imbalance of monocyte function could be partly the result of a decrease in HO-1 expression, which might be related to pathogenesis of SLE [41]. The change of HO-1 in patients with SLE is considered attribute to the fragility of patients to common stressful stimuli, such as viral infections, toxic substances, lipopolysaccharides, and their enhanced susceptibility to endothelial damage [42,43].

Therefore, targeting HO-1 and modulating HO-1 related signaling is prospective for SLE treatment.

4.2. Rheumatoid arthritis

The effect of HO-1 in rheumatic diseases could be further confirmed in rheumatoid arthritis. RA is a systemic inflammatory disease characterized by chronic inflammation resulting in synovial hyperplasia, articular cartilage and marginal bone damage and joint destruction [44–46]. Even numerous progressive treatment strategies could ameliorate the progression of the disease, RA still remains incurable and needs new therapies. Oxidative stress is one of several mechanisms triggering immune activation which is associated with the pathogenesis of RA [47]. As reported, HO-1 was remarkably induced in inflamed tissues in a collagen-induced arthritis (CIA) model [48]. Besides, HO-1 was demonstrated to be highly expressed in peripheral blood monocytes, synovial tissues and synovial fluid of rheumatoid arthritis patients [49–51]. Interestingly, induction of HO-1 suppresses osteoclastogenesis and bone destruction in a TNF-α mediated arthritis [52]. Furthermore, levels of bilirubin in serum, which is a metabolite of HO-1, were elevated in patients of RA [52].

4.3. Osteoarthritis

OA is a prevalent aging-related chronic joint disorder featured by degradation and destruction of the extracellular matrix of articular cartilage, subchondral bone sclerosis, synovial membrane thickening and osteophyte formation [53–55]. Recently, oxidative stress has been established as a crucial factor as it is increased in articular cartilage and other components of musculoskeletal system in OA [56,57]. In view of the regulate role of HO-1 in oxidative damage, the potential effect of HO-1 in pathogenesis of OA has attracted more attention. In aging and OA, oxidative damage is distinctly elevated in cartilage. It is also found that HO-1 was significantly reduced in articular cartilage with aging in wild-type mice [58]. All these results hint that maintenance of HO-1 may have potential to protect from OA development.

5. Therapeutic strategy targeted HO-1

Based on the researches focusing on the effect of HO-1 in rheumatic diseases, amount of approaches targeting regulation of HO-1 have been arising (See Table 1 for summary). It has been shown that different strategies such as gene therapy, pharmacologic modulation of HO-1 or administration of metabolic products of HO-1 can display salutary cytoprotective and immunoregulatory effects [6,59]. Many pharmacological compounds, for instance, resveratrol, polyphenols, carnosol and curcumin, which are targeting up-regulation of HO-1 has shown specific anti-inflammatory and antioxidant effects in rheumatic diseases including SLE, arthritis and psoriasis [60–62]. Moreover, administration of CO, which is a main product of HO-1, also displays beneficial effects in rheumatic diseases treatment [63,64].

Currently, the major strategies modulating expression of HO-1 mainly consist of chemical induction and molecular biology technique. The chemical substances, hemin, NO, Simvastatin and metalloporphyrin are generally used for regulating HO-1 expression. With regard to molecular biology technology, siRNA or gene knock-out is the most commonly used method, which can furthest limit the expression of HO-1. On the other hand, transfection of HO-1 vector or Bach1 knock-out can lead to HO-1 overexpression.

5.1. HO-1 as a target for therapies of SLE

Takeda et al. showed that the administration of hemin, an HO-1 inducer, suppressed nitric oxide (NO) dependent inflammatory responses and reduced pathogenic anti-dsDNA immunoglobin levels as well as ameliorates nephritis severity manifesting as reduced glomerular immune complexes in the MRL-Fas*lpr* mouse model of lupus [65]. FcγRIIb-deficient mice are considered as an SLE animal model because increased susceptibility to B cell activation responding to immune complexes [66]. It is confirmed that FcγRIIb-deficient SLE mice display significantly decrease of expression of HO-1 in the spleen. However, CO treatment reverses the expansion of $CD11b^+$ cells and contraction of $CD4^+Foxp3^+$ [regulatory T (Treg)] cells and decreases anti-histone IgG levels. More importantly, exposure to CO alleviates renal damage and proteinuria of FcγRIIb-deficient mice [63]. Recently, Yohei Kirino et al. found Bach1 negatively regulates HO-1 expression and M2 Mϕ polarization, leading to the inflammation of LN, and HO-1 upregulation by genetic ablation of Bach1 can ameliorates LN in mice [67].

Patients with SLE usually have a variety of syndromes including coronary artery disease and central nervous system (CNS) deficiency [68,69]. Nowadays, some studies have discovered that HO-1 has the capacity to restore homeostasis to reverse the disorder induced by coronary artery disease [42]. Moreover, HO-1 also exhibits possible neuroprotective effects due to the anti-inflammatory, anti-apoptotic, and vasodilatory properties of CO, which is one of the products of HO-1 [70,71].

Table 1
Main mode of action of HO-1 performed in rheumatic diseases.

Diseases	Agent or manipulation	Property	Results and mechanisms	Ref no.
SLE	Hemin	Induction of HO-1	HO-1 ameliorated lupus nephritis. HO-1 suppressed iNOS expression in the kidney. HO-1 reduced pathogenic anti-dsDNA immunoglobin levels, glomerular immune complexes and serum IFNγ.	[65]
	CO treatment	Induction of HO-1	HO-1 decreases the expansion of CD11b + cells and anti-histone IgG levels, but increases contraction of Treg cells.	[63]
	$Bach1^{-/-}$	Induction of HO-1	Dysregulated $HO\text{-}1^{low}$ M2 macrophages contribute to augmenting the inflammation of lupus nephritis. Supplementation of HO-1 by targeting Bach1 genes prolonged survival, reduced urine proteins, and serum blood urea nitrogen levels.	[67]
RA	CO and biliverdin	Induction of HO-1 and increased biliverdin	HO-1 ameliorated clinical signs of CIA including decreased serum anti-collagen antibodies and mitigated cartilage erosion.	[72]
	CORM-3	Increased CO	Reduced joint inflammation and erosion.	[73]
	CoPP	Induction of HO-1	HO-1 diminished clinical signs, cartilage erosion and proinflammatory cytokine production in the K/BxN mouse arthritis model and CIA arthritis model.	[48] [74]
	SnPP	Inhibition of HO-1	More effective than CoPP in preventing the development of CIA. Decreased leukocyte infiltration, hyperplastic synovitis, articular cartilage, osteolysis and production of inflammatory mediators in rat adjuvant arthritis experiment model.	[48] [75]
OA	$Bach1^{-/-}$	Increased expression of HO-1	Highly increased expression of HO-1 in articular cartilage protected mice from progression of OA.	[58]
	HO-1 siRNA	Knock down expression of HO-1	The protective effect of Bach1 deficiency was lost.	[58]
SSc	CoPP	Induction of HO-1	Restore HO-1 levels and change the increased TLR response.	[76]

5.2. HO-1 as a target for therapies of RA

In an collagen-induced arthritis model, the administration of products of heme degredation, CO and biliverdin, ameliorated clinical signs of arthritis including decreasing serum anti-collagen antibodies and mitigating cartilage erosion [72]. Moreover, treatment with a CO-releasing molecule-3 (CORM-3) reduced joint inflammation and erosion in murine collagen-induced arthritis [73]. All these evidences show that induction of HO-1 and its metabolism products may have a potential protective effect in RA.

More interestingly, another research found that cobalt protoporphyrin IX (CoPP), an inducer of HO-1, could lead to diminish clinical signs, cartilage erosion and proinflammatory cytokine production in the K/BxN mouse arthritis model and CIA arthritis model [48,74]. However, tin protoporhyrin IX (SnPP), a HO-1 inhibitor, turned out to be more effective than CoPP in preventing the development of CIA [48]. The results showed CoPP treatment inhibited TNF-α and IL-2 levels but failed to modify IL-1β. While the production of IL-10 was reduced, which participate in the suppression of arthritis during murine CIA [48].

In another rat adjuvant arthritis experiment model, administration of HO-1 inhibitor SnPP also showed therapeutic effects including decreased leukocyte infiltration, hyperplastic synovitis, articular cartilage, osteolysis and production of inflammatory mediators [75]. In this study, the inhibition of HO-1 partially decreased iNOS expression and NO production, directly attributed to regulation of inflammatory cytokines such as TNF-α and IL-1.

It is interesting to note that there are a few of researches suggest that the protective effects of induction of HO-1 on cartilage are lower than those of inhibition of HO-1. It is may be due to the different regulation mode of CoPP on cytokines in different models.

5.3. HO-1 as a target for therapies of osteoarthritis

Tsuyoshi Takada et al. showed that Bach1$^{-/-}$ mice, which exhibited highly increased expression of HO-1 in articular cartilage, protected mice from progression of OA in primary aging and post-traumatic models of the disease [58]. However, when chondrocytes were treated with small interfering RNA against HO-1, the protective effect of Bach1 deficiency was lost [58]. It is suggested that maintenance of HO-1 may be beneficial for prevention of OA development in both aging and post-traumatic OA.

5.4. Other rheumatic conditions

Lenny van Bon et al. have discovered that low plasma levels of bilirubin and HO-1 expression in immune cells from Systemic sclerosis (SSc) patients. Induction of HO-1 with CoPP can restore HO-1 levels and change the increased Toll-like receptor (TLR) response [76].

6. Conclusions and perspectives

HO-1 has been identified as an important factor with respect to a number of physiologic systems because of its characteristic anti-inflammatory and anti-oxidative role. Due to the different expressions and various functions of HO-1 in disparate cells and tissues, there are still many confused and intricate mechanisms about how HO-1 function in related disorders. The salutary antioxidant and anti-inflammatory effects of HO-1 appear to be critically dependent on its concentration and intensity, and inappropriate activation of HO-1 may result in undesirable immunosupression [77]. So it is essential to monitor the HO-1 expression during different phases of the disorders, and levels of HO-1 in different tissues and organs should be further confirmed in order to correlate it with clinical symptoms and other hallmarks of rheumatic diseases.

Remarkably, some studies indicate that the enzymatic action of HO-1 is not always related to beneficial effects. For instance, iron, which is released by HO-1 activity, may contribute to lipid peroxidation and even tissue damage [78,79]. Besides, induction of HO-1 by hypoxia/re-oxygenation and resulting activation of CO/cGMP pathway make a difference to stimulus for macrophage activation, synthesis and release of pro-inflammatory cytokines [80]. HO-1 inhibition also exerts antioxidant effects in some experimental models, such as SJL mice with experimental allergic encephalomyelitis and rat adjuvant arthritis [75,79]. Nevertheless, recent studies suggest the importance of HO-1 goes beyond its enzymatic activity [81]. Particularly, the immunoreactive forms of HO-1 in the nucleus which lack catalytic activity have been proposed to contribute to transcriptional regulation.

There were few reports about how HO-1 system functioned in rheumatic diseases from clinical trials, we presented recent investigation mainly on three typical diseases and respective animal models, which the HO-1 regulatory mechanism associated with, among more than 100 rheumatic diseases. We hope that our review could intrigue scientists and physicians to find out the exact role of HO-1 in rheumatic diseases.

Abbreviations

HO-1	Heme oxygenase-1
CO	Carbon monoxide
BR	Biliverdin
HO	Heme oxygenase
ROS	Reactive oxygen species
CoA	Coenzyme A
ALA	Aminolevulinic acid
FtH	Ferritin heavy chain
Keap1	Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1
Nrf2	Nuclear factor erythroid 2-related factor 2
ARE	Antioxidant Response Elements
HMOX1	Hemeoxygenase 1
NQO1	NAD(P)H quinone oxidoreductase 1
GCL	Glutamate-cysteine ligase
GSTs	Glutathione S transferases
Bach1	BTB and CNC homologue1
PAMPs	Pathogen-associated molecular pattern
DAMPs	Damage-associated molecular pattern
MAPK	Mitogen-activated protein kinases
JNK	c-Jun N-terminal kinases
miRNAs	microRNAs
SLE	Systemic lupus erythematosus
RA	Rheumatoid arthritis
OA	Osteoarthritis
UV	Ultraviolet light
CIA	Collagen-induced arthritis
CAT	Catalase
SOD	Superoxide dismutase
GPx	Glutathione peroxidase
NO	Nitric oxide
CNS	Central nervous system
CORM-3	CO-releasing molecule-3
CoPP	cobalt protoporphyrin IX
SnPP	tin protoporhyrin IX
SSc	Systemic sclerosis
TLR	Toll-like receptor

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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