A novel hypothesis: up-regulation of HO-1 by activation of PPARγ inhibits HMGB1-RAGE signaling pathway and ameliorates the development of ALI/ARDS

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ABSTRACT

Suppression of inflammation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) by activation of peroxisome proliferator-activated receptor (PPAR)-γ has been well demonstrated in animal model studies. However, the molecular mechanisms underlying this effect remain largely unknown. The induction of heme oxygenase-1 (HO-1) exerts antioxidant, anti-apoptotic, and immunomodulatory functions in various situations. Recent studies have indicated that activation of PPARγ induces expression of HO-1, suggesting that HO-1 is a downstream target of PPARγ. Meanwhile, study has shown that activation of PPARγ ameliorates inflammatory response of cells by inhibiting high mobility group box 1 (HMGB1) release. In pulmonary system, binding of HMGB1 to its receptor for advanced glycation end-products (RAGE) triggers the production of pro-inflammatory cytokines, chemokines, adhesion molecules and reactive oxygen species, promoting the development of ALI/ARDS. Based on the recent findings that induction of HO-1 protects tissues and cells from extracellular stress by reducing HMGB1 production, we propose the hypothesis that HO-1 may mediate the protective effects of PPARγ on inhibition of HMGB1-RAGE signaling pathway to attenuate the development of ALI/ARDS.

KEYWORDS

Peroxisome proliferator-activated receptor (PPAR)-γ; heme oxygenase-1 (HO-1); high mobility group box 1 (HMGB1); receptor for advanced glycation end-products (RAGE); acute lung injury/acute respiratory distress syndrome (ALI/ARDS)

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Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are well defined and readily recognized clinical disorders caused by many clinical insults to the lung or because of predispositions to lung injury (1). The reported frequency of acute lung injury varies from 1.5 to 75 cases per 100,000 populations (2,3). The pathogenesis of ALI/ARDS involves the imbalance of oxidant/antioxidant, inflammation/anti-inflammation, and the up-regulation of adhesion molecules and chemokines. These changes cause a variety of pathological alterations in lung, which include accumulation of large numbers of neutrophils in alveolus, increased apoptosis of endothelial and alveolar epithelium cells, increased permeability of capillary endothelial and the development of interstitial edema (4). Despite a lot of efforts have been made to manage these conditions, the mortality of ALI/ARDS is still high (5,6). Therefore, there is an urgent requirement to set up a new approach and search for an effective medicine to control these conditions.

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The intrinsic protective mechanisms in lung

PPARγ

Peroxisome proliferator-activated receptors (PPARs) belong to a nuclear hormone receptor superfamily, and are classified into three isoforms, including α, β/δ, and γ. With the binding of agonists, PPARs are activated and translocate to the nucleus to regulate the particular genes transcription through binding to PPAR response element (PPRE). The function of PPARs *in vivo* is to modulate lipid/lipoprotein metabolism and adipogenesis, glucose homeostasis, cell cycle progression and cellular proliferation/differentiation (7).

The expression of PPARγ has been found in infiltrated inflammatory cells and structural cells of the lung (8). Recent *in vivo* and *in vitro* studies have shown that activation of PPARγ demonstrates the functions of anti-inflammation, immunomodulation and inhibition of cell proliferation, indicating that the activation of PPARγ might have a potential value in the treatment of ALI/ARDS, asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) (9-12). Clinic evidence suggests that patients with diabetes show a reduced risk for lung injury (13). Although the mechanisms for this phenomenon are complex, usage of PPARγ agonist might be associated with this protection (13).

HO-1

Heme oxygenase (HO) is the rate-limiting enzyme which degrades heme into carbon monoxide (CO), iron and biliverdin (14). To date, three isoforms of HO (e.g., HO-1, HO-2, HO-3) have been identified. HO-1 is an inducible form of HO which is normally expressed at low levels in most tissues, it's expression is induced by a variety of pathophysiologic stimuli such as hypoxia, inflammation and endotoxin exposure (15,16). The induction of HO-1 protects mammals against inflammatory response and oxidant stress by production of CO and biliverdin and its metabolite, bilirubin (17). Induction of HO-1 has also been shown to ameliorate the lung injury induced by lipopolysaccharide (LPS) in animal studies, suggesting that HO-1might be a new target by enhancing its function to treat ALI/ARDS (18,19).

Up-regulation of HO-1 by PPARγ

Recent studies in vascular endothelial and smooth muscle cells have shown that induction of HO-1 confers the protective role of activation of PPARγ against a variety of stresses (20,21). Kronke *et al.* (20) reported that, upon ligand binding, PPARγ moves to nucleus, binds to the promoter of HO-1 and promotes HO-1 expression. Evidence has also shown that induction of HO-1 up-regulates the expression of PPARγ (22), suggesting that a positive loop has been formed between PPARγ and HO-1, enhancing the protective roles of PPARγ. However, it is still unclear whether activation of PPARγ stimulates the expression of HO-1 in lung to ameliorate the development of ALI/ARDS. If this protective mechanism exists in ALI/ARDS, then which downstream targets are further regulated by HO-1?

Role of HMGB1-RAGE signaling pathway in inflammatory response

High mobility group box 1 (HMGB1)

HMGB1 was initially defined as a nuclear protein which loosely binds to chromatin, and plays a pivotal role in bending DNA and regulating transcription (23). Under conditions of infection, injury and sterile inflammation, HMGB1 is either passively released from injured or necrotic cells or actively secreted by immune cells stimulated by cytokine and endotoxin (24). Although the role of HMGB1 in the nucleus is not completely understood, the function of HMGB1 in extracellular has been found to be associated with inflammatory responses.

Receptor for advanced glycation end-products (RAGE)

The RAGE is a member of immunoglobulin superfamily of cell surface receptors expressed in various cell types (25). The pulmonary system has a relatively high expression of RAGE (26), especially in type I alveolar epithelial cells (27,28). In response to inflammation, the expression of RAGE is dramatically induced in type I alveolar epithelial cells and infiltrated inflammatory cells (29), suggesting that RAGE might have an important role in lung pathophysiology. RAGE is a multiligand-binding receptor, which can bind with advanced glycation end products (AGEs), Amyloid β-peptide, S100 proteins, and HMGB1 (30).

The role of HMGB1-RAGE cascade in inflammation

Accumulative evidences have shown that extracellular HMGB1 is a critical proinflammatory cytokine, which can bind to particular receptors, including RAGE, TLR2 and TLR4, on target cells to induce the production of proinflammatory cytokines, chemokines, adhesion molecules and reactive oxygen species, leading to inflammation and injury (24,30-32). Further studies have suggested that binding of HMGB1 to its receptor RAGE activates NF-κB (33) and MAPK (34) signaling pathways which mediate the production of a variety of proinflammatory mediators, such as TNF-α, IL-1β and HMGB1 and RAGE themselves. This indicates that activation of HMGB1-RAGE cascade amplifies the inflammatory responses *in vivo* and exacerbates the tissue damage, and also suggests that HMGB1-RAGE signal plays a central role in the development of inflammatory diseases.

The involvement of HMGB1-RAGE signal in ALI

HMGB1-RAGE signal has been shown to play a critical role in the development of acute lung injury. The level of HMGB1 is elevated in mice exposure to endotoxin, and is associated with tissues injury (including lung) and endotoxin lethality (35,36). Neutralization of HMGB1 suppresses LPS-induced pulmonary inflammation and lung injury (37). Mice lacking RAGE have resistance to endotoxemia, and show protection against lung injury (38). The biological rationale and encouraging results in animal study suggest an essential role of HMGB1-RAGE pathway in the pathogenesis of ALI. Translational research

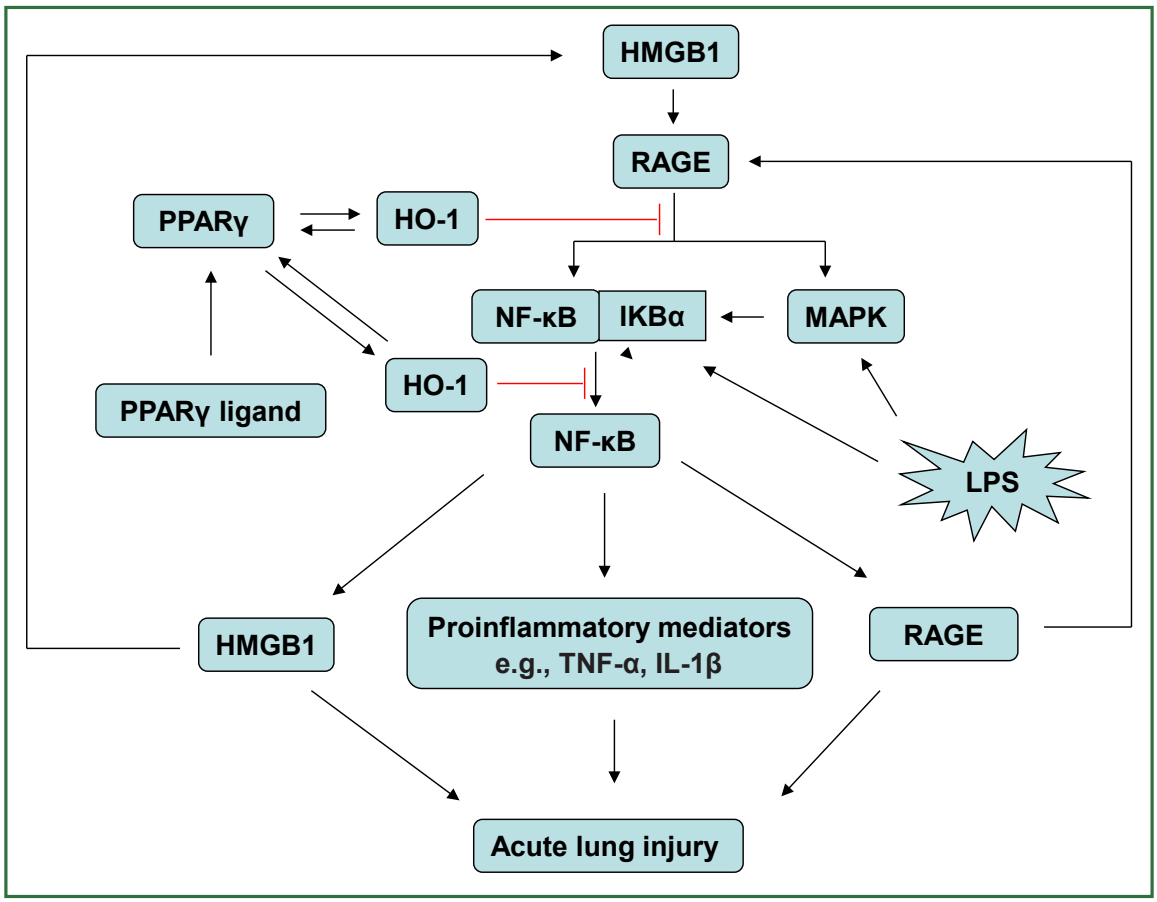

Figure 1. Proposed scheme of the effects of up-regulation of HO-1 by PPARγ activation on HMGB1-RAGE signaling pathway in ALI/ARDS. Interaction of HMGB1 with RAGE activates the NF-κB and MAPK pathway, resulting in the up-regulation of HMGB1, RAGE and other proinflammatory mediators and promoting the development of ALI/ARDS. Activation of PPARγ induces HO-1 expression and subsequent suppression of HMGB1-RAGE signaling pathway. Therefore, we hypothesize that up-regulation of HO-1 by activation of PPARγ might inhibit HMGB1-RAGE signaling pathway and ameliorate the development of ALI/ARDS.

is further needed to verify that targeting HMGB1-RAGE is effective in clinic for the treatment of ALI/ARDS.

Hypothesis

There is a growing body of evidences to demonstrate that activation of PPARγ induces the expression of HO-1 which further plays a variety of protective roles in vascular system (20,21). Recent evidence suggests that activation of PPARγ ameliorates inflammatory response of cells by inhibiting HMGB1 release (39). At the same time, other study indicates that induction of HO-1 protects tissues and cells from extracellular stress by reducing HMGB1 production (40,41). Giving the fact that HMGB1-RAGE signaling pathway is associated with the development of ALI/ARDS and other inflammatory diseases (24,30-32,42), we propose the hypothesis that up-regulation of HO-1 by activation of PPARγ inhibits HMGB1-RAGE signaling pathway and ameliorates the development of ALI/ARDS (Figure 1).

However, this is only a hypothesis; it still needs to be verified by preclinical and clinical studies. If this protective effect exists in pulmonary system, it will provide a novel avenue to treat ALI/ARDS.

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