Inflammopharmacology (2022) 30:811–820
https://doi.org/10.1007/s10787-022-00988-y

Inflammopharmacology

REVIEW

High-mobility group box 1 (HMGB1) in COVID-19: extrapolation of dangerous liaisons

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Received: 16 January 2022 / Accepted: 30 March 2022 / Published online: 26 April 2022

Abstract

High-mobility group box 1 (HMGB1), a multifunctional nuclear protein, exists mainly within the nucleus of all mammal eukaryotic cells. It is actively secreted by the necrotic cells as a response to the inflammatory signaling pathway. HMGB1 binds to receptor ligands as RAGE, and TLR and becomes a pro-inflammatory cytokine with a robust capacity to trigger inflammatory response. It is a critical mediator of the pathogenesis of systemic inflammation in numerous inflammatory disorders. Release of HMGB1 is associated with different viral infections and strongly participates in the regulation of viral replication cycles. In COVID-19 era, high HMGB1 serum levels were observed in COVID-19 patients and linked with the disease severity, development of cytokine storm (CS), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). SARS-CoV-2-induced cytolytic effect may encourage release of HMGB1 due to nuclear damage. Besides, HMGB1 activates release of pro-inflammatory cytokines from immune cells and up-regulation of angiotensin I-converting enzyme 2 (ACE2). Therefore, targeting of the HMGB1 pathway by anti-HMGB1 agents, such as heparin, resveratrol and metformin, may decrease COVID-19 severity. HMGB1 signaling pathway has noteworthy role in the pathogenesis of SARS-CoV-2 infections and linked with development of ALI and ARDS in COVID-19 patients. Different endogenous and exogenous agents may affect release and activation of HMGB1 pathway. Targeting of HMGB1-mediated TLR2/TLR4, RAGE and MAPK signaling, might be a new promising drug candidate against development of ALI and/or ARDS in severely affected COVID-19 patients.

Keywords Anti-HMGB1 agents · High-mobility group box 1 · SARS-CoV-2 · COVID-19 · Acute respiratory distress syndrome

Background

High-mobility group box 1 (HMGB1) is a nuclear protein that binds with DNA as a chromatin binding factor, and involved in DNA repair and control of replication process (Paudel et al. 2019). HMGB1 supports cell survival through activation of autophagy through interaction with anti-apoptotic protein (Tong et al. 2018). It is released from the cells during necrosis and as a response to the inflammatory signaling pathway (Shah et al. 2019; Alsousi and Igwe 2018). The intracellular HMGB1 is released out of cells through activation of nuclear factor kappa B (NF-κB) signaling pathway (Kim et al. 2018). Extracellular HMGB1 activates receptor for advanced glycation end-product (RAGE) and toll-like receptors (TLRs) (Yao et al. 2018). HMGB1 is secreted from immune cells like monocytes, macrophages and dendritic cells by specific secretory pathway as a cytokine mediator (Richard et al. 2017). Excess release of

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HMGB1 from activated immune cells mainly macrophages is associated with tissue damage as in ischemia, arthritis, endotoxemia and sepsis (Andersson et al. 2018). In addition, HMGB1 is translocated into the cytosol due to oxidative stress and high reactive oxygen species (ROS) (Tang et al. 2011). Various pathogens, like bacterial and viral infections may induce passive release of HMGB1 leading to release of pro-inflammatory cytokines and critical systemic inflammation (Wang et al. 2006).

High HMGB1 serum level has been reported in COVID-19 patients and linked with disease severity, development of cytokine storm (CS), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Street 2020). Thus, the aim of the present perspective was to elucidate the potential role of HMGB1 in the pathogenesis of SARS-CoV-2 infection and to scrutinize anti-HMGB1 agents as possible new therapeutic modality in the management of COVID-19.

HMGB1 and respiratory viral infections

Induction of HMGB1 release is associated with different viral infections; Simpson et al. (2020) showed that acute bronchiolitis caused by respiratory syncytial virus (RSV) is correlated with high HMGB1 in the nasopharyngeal samples in children. RSV is regarded as the main cause of severe lower respiratory tract infections in children and linked with mortality in the elderly (Moriyama et al. 2020). RSV-mediated acute respiratory dysfunction is arbitrated to induction of oxidative stress and activation of HMGB1 pathway (Hosakote et al. 2016). During viral infections, HMGB1 has been shown to induce the phosphorylation of NF-κB and mitogen-activated protein kinase (MAPK) in the respiratory epithelial cells. Besides, HMGB1 activates release of pro-inflammatory cytokines from immune cells (Hosakote et al. 2016). Interestingly, viral molecules during respiratory infections activate pattern recognition receptors (PRRs) on the immune and lung epithelial cells that contribute to the augmentation and exacerbation of inflammation. Of interest, damage-associated molecular patterns (DAMPs) from necrotic cells like HMGB1 stimulate PRRs mainly RAGE and TLRs leading to induction of inflammatory cascade and disease exacerbation during respiratory viral infections (Hosakote et al. 2016). Indeed, binding of HMGB1 to the nucleoprotein of influenza virus in the infected cells enhances virus RNA-dependent polymerase activity and virus proliferation. Therefore, blocking binding of HMGB1 to the viral nucleoprotein might be a potential target in the management of influenza-induced complications (Moisy et al. 2012). As well, dengue virus mediates release of HMGB1 from monocytes and linked with the pathogenesis of endothelial injury as indicated by maintenance of the vascular barrier integrity after treatment with HMGB1 neutralizing antibody (Ong et al. 2012).

Previously, in SARS-CoV pandemic, HMGB1 was identified as a potential mediator in early severe local pulmonary inflammation and late critical systemic inflammation, and anti-HMGB1 antibody was used in the management of SARS pandemic (Chen et al. 2004). Therefore, HMGB1 is regarded as an imperative mediator in respiratory viral infections and their associated complications.

HMGB1 in acute lung injury

Acute lung injury (ALI) is a critical respiratory disorder characterized by severe lung inflammation and pulmonary vascular injury and/or permeability leading to hypoxemia and multi-organ damage (MOD) (Tsushima et al. 2009). ALI may be a consequence of different pathological conditions including, respiratory infection, trauma, aspiration, shock, and burns, it is associated with 40% mortality in intensive care unit (ICU) patients (Kellner et al. 2017). Various inflammatory cascades are involved in the pathogenesis of ALI and related interstitial pulmonary edema through cytokine release with consequent activation and recruitment of neutrophils and myeloperoxidase secretion. (Buesing et al. 2011). HMGB1 is a prognostic biomarker and potential target in ALI, because it reflects a degree of tissue inflammation as well as its potency in blocking inflammatory pathways. Further, HMGB1 is regarded as a late inflammatory mediator in the pathogenesis of ALI via induction of NF-κB signaling pathway, which further induces release of HMGB1 in a positive feedback loop (Ding et al. 2021).

Initiation of ALI is started when extracellular HMGB1 activates cell membrane TLR2, TLR4 and RAGE receptors. Activation of RAGE receptors leads to triggering of ROS-dependent activation of MAPK pathway (Al-Kuraishy et al. 2021c; Jia et al. 2020). Though, activations of TLR2 and TLR4 by HMGB1 trigger activations of intracellular myeloid differentiation 88 (MyD88), which activates inhibitor of nuclear factor kappa B kinase (IKK-β) (Al-Kuraishy et al. 2021c). Both of IKK-β and MAPK stimulate NF-κB signaling pathway; however, extracellular HMGB1 may directly activate NF-κB through phosphatidyl-inositol 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) independent of TLRs or RAGE receptors (Qu et al. 2019a). The interaction between HMGB1 and RAGE enhances the release of platelet derived growth factor (PDGF), transforming growth factor (TGF) and other fibrinogen mediators in the pulmonary tissue that result in ALI (Zou et al. 2018) (Fig. 1). Besides, HMGB1 may induce ALI through activation of autophagy, which causes release of inflammatory cytokines from neutrophils and macrophages, as well autophagy of epithelial and endothelial cells leading to

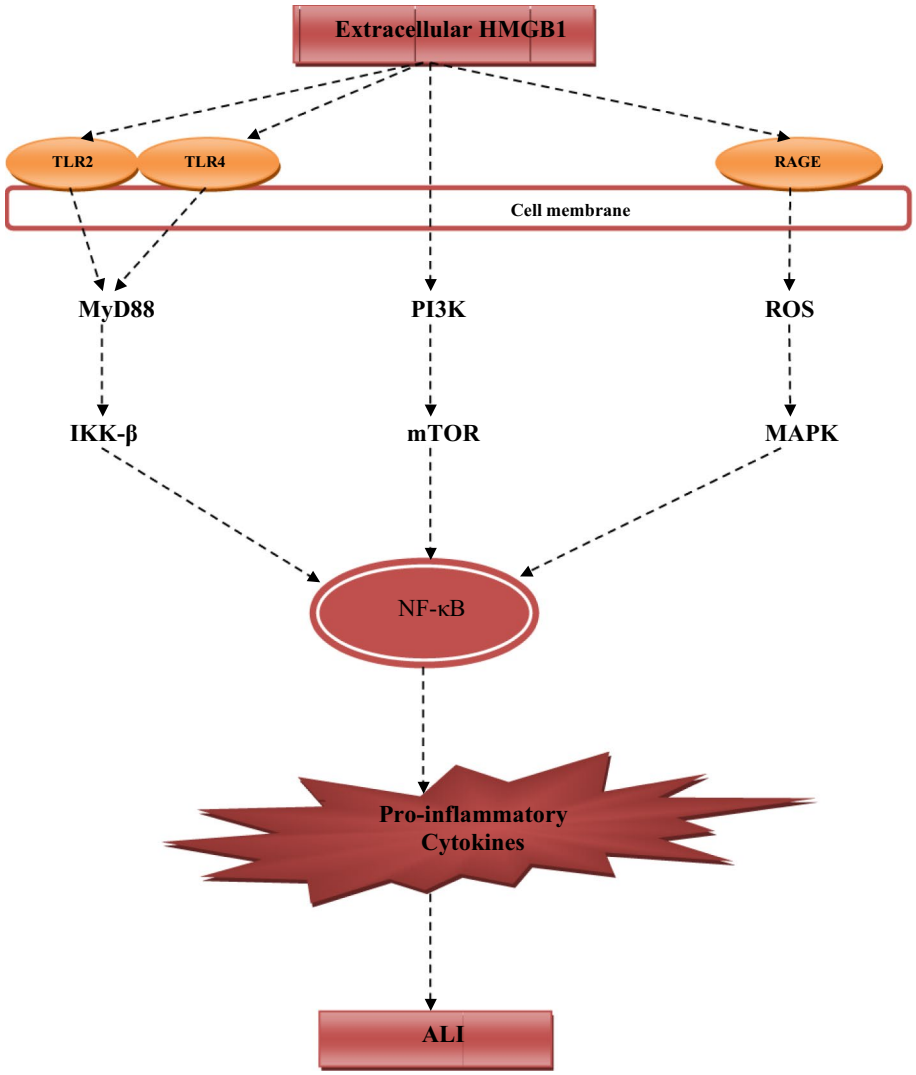

Fig. 1 Role of HMGB1 in the development of acute lung injury (ALI): extracellular high-mobility group box 1 (HMGB1) activates cell membrane TLR2, TLR4 and RAGE receptors. Activation of RAGE receptors leads to triggering of ROS-dependent activation of MAPK pathway. Though, activations of TLR2 and TLR4 by HMGB1 trigger activations of intracellular myeloid differentiation 88 (MyD88), which activates inhibitor of nuclear factor kappa B kinase (IKK-β). Both of IKK-β and mitogen-activated protein kinase (MAPK) stimulate NF-κB signaling pathway. However, extracellular HMGB1 may directly activate NF-κB through phosphatidyl-inositol 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) independent of TLRs or RAGE receptors leading to release of pro-inflammatory cytokines that result in ALI

release of chemokines and increased permeability, respectively (Qu et al. 2019a). Therefore, HMGB1 blood level might be a surrogate biomarker of ALI induced by different etiology.

HMGB1 in COVID-19

SARS-CoV-2 is an enveloped positive sense RNA virus belongs to *betacoronaviridiae*, has high reproductive number and responsible for human respiratory infection. SARS-CoV-2 binds to the integral membrane protein named angiotensin-converting enzyme 2 (ACE2) by viral surface protein (SP) (Al-Kuraishy and Al-Gareeb 2020). This binding is facilitated by a cellular trypsin-like protease, transmembrane protein serine 2 (TMPRSS2) (Alshahawey et al. 2020). The interaction between SARS-CoV-2 and ACE2 is associated with increasing in the vasoconstrictor angiotensin II (AngII) and reduction in the vasodilator Ang1-7 and Ang1-9 due to down-regulation of ACE2 (Al-Kuraishy et al. 2020c). SARS-CoV-2-induced deregulation of renin–angiotensin system (RAS) evokes notable disturbances in pulmonary hemodynamic and oxygen saturation (Al-Kuraishy et al. 2020b). SARS-CoV-2 mainly affects alveolar epithelial cell type II (AECII) leading to over-secretion of chemokines and inflammatory cytokines, such as IL-1β, IL-18, IL-6, and chemokine ligand 5 (CCL5) (Al-Kuraishy et al. 2020a). Besides, tumor necrosis factor alpha (TNF-α) and monocyte chemoattractant protein 1 (MCP-1) from activated macrophages augment AECII damage and may increase viral entry (Al-Kuraishy et al. 2021b). Therefore, exacerbation of immune response in SARS-CoV-2 infection may cause severe infection and cytokine storm with development of ALI and ARDS (Al-Kuraishy et al. 2021a).

Moreover, high pro-inflammatory cytokines with activation of NF-κB signaling pathway trigger the release of HMGB1 from monocytes and macrophages (Zou et al. 2020). As well, HMGB1 is also released from infected

or necrotic non-immune cells (Klune et al. 2008). It has been proposed that SARS-CoV-2-induced cytolytic effect may encourage release of HMGB1 due to nuclear damage (Wyganowska-Swiatkowska et al. 2020). Of note, extracellular HMGB1 through activation of NF-κB signaling pathway provokes cytokine release and substantial neutrophil infiltrations into the lung with subsequent development of ALI and/or ARDS (Wyganowska-Swiatkowska et al. 2020).

It has been shown that HMGB1-mediated autophagy is involved in in the pathogenesis of ALI in SARS-CoV-2 infection (Sun 2020). Yang and Shen (2020) illustrated that autophagy and endocytic pathway are incorporated in SARS-CoV-2 infections and linked with COVID-19 severity. In addition, over-expression of ACE2 is associated with lower release of HMGB1 (Qi et al. 2016), herein, down-regulation of ACE2 during SARS-CoV-2 infections may contribute into the release of HMGB1 and associated hyper-cytokinemia in ALI (Stilhano et al. 2020). Besides, SARS-CoV-2 may directly activate node-like receptor pyrin 3 (NLRP3) inflammasome, which through Janus kinase/signal transducer of transcription protein 1 (JAK/STAT1) triggers the release of HMGB1 from nucleus to the cytoplasm (Freeman and Swartz 2020). Therefore, inhibition of NLRP3 inflammasome and JAK/STAT1 signaling pathway may reduce release of HMGB1 and associated inflammatory reactions (Wang et al. 2017). Moreover, high circulating HMGB1 in diabetic patients predisposes them for high pro-inflammatory cytokine reactions and COVID-19 severity (Biscetti et al. 2019, Bloomgarden 2020). Indeed, the interaction between HMGB1 and RAGE receptors is mainly linked with development of ALI/ARDS in COVID-19 through injury of lung epithelial barriers and induction of endothelial permeability with development of pulmonary edema (Kerkeni and Gharbi 2020). Besides, soluble RAGE receptors are increased in the circulation of COVID-19 patients with ARDS (Chiappalupi et al. 2021).

Regarding HMGB1 serum level in COVID-19 patients and clinical outcomes, Chen et al. (2020) reported that critically patients in ICU have high circulating HMGB1, which correlated with poor clinical outcomes and high mortality. Severe COVID-19 infection is commonly associated with coagulopathy and thrombosis due to endothelial injury and development of CS (Ackermann et al. 2020). It has been reported that HMGB1 is regarded as a critical mediator of thrombosis through platelet activations, stimulation of inflammatory reactions, neutrophil recruitment, and induction of micro-thrombosis and formation of neutrophil extracellular traps (NETs) (Vogel et al. 2015). Therefore, HMGB1-induced thrombosis and CS are associated with development of ARDS in severe SARS-CoV-2 infections (Lupu et al. 2020). Herein, HMGB1 is regarded as the main player in SARS-CoV-2 infection in the initiation of hyper-cytokinemia, CS and immune-thrombosis that mediate development of ALI and ARDS (Fig. 2). Therefore, targeting of HMGB1 by conventional drugs or herbal medicine might be a potential therapeutic modality in the management of COVID-19.

Extracellular HMGB1 inhibitors

Different experimental, preclinical, and clinical studies illustrated that HMGB1 inhibitors reduced markedly the inflammatory conditions driven by HMGB1 in a broad set of inflammatory disease models (Yang et al. 2020). Therefore, we discussed some of HMGB1 antagonists, and how they could produce therapeutic effects through inhibition of HMGB1 pathway. It is noteworthy that these compounds are not HMGB1-specific, but they have the capacity to suppress HMGB1-triggered inflammation and other recognized bioactivities. Except for chloroquine and glycyrrhizin, the direct anti-viral effects of these compounds are not proven yet.

Statins

Statins are competitive inhibitors of 3-hydroxyl-3-methylglutaryrl Co-enzyme A (HMG-CoA) with cholesterol-lowering effect, used in the management of dyslipidemia and cardio-metabolic disorders (Kadhim et al. 2020). Statins also have significant anti-inflammatory, anti-thrombotic, and anti-platelet activities (Hussien et al. 2021). It has been shown that statins inhibit the interaction of HMGB1 with both TLR4 and RAGE receptors, in addition to inhibition of the expression of TLR4 and RAGE receptors in different inflammatory disorders (Yang et al. 2010). Therefore, statins could attenuate the effect of HMGB1 that is mediated by TLR4 and RAGE receptors. Kong et al. (2016) illustrated that statins suppress NLRP3 inflammasome via inhibition of TLR4/MyD88/NF-κB signaling pathway. Thus, statins may attenuate SARS-CoV-2 infection-induced pro-inflammatory cytokine reaction and COVID-19 mortality (Permana et al. 2021). However, meta-analyses of observational studies illustrated that COVID-19 patients who received statins therapy did not show marked decline in either hospital mortality or the COVID-19 severity (Scheen 2021). Nonetheless, statins therapy improves clinical outcomes in COVID-19 through modulation of cellular processes and inflammatory mediators, such as autophagy, NLPR3 inflammasome and up-regulation of ACE2, that collectively block release and activation of HMGB during SARS-CoV-2 infection (Rodrigues-Diez et al. 2020).

Chloroquine

Chloroquine/hydroxychloroquine compounds have been reported to effectively abrogate the COVID-19 infection

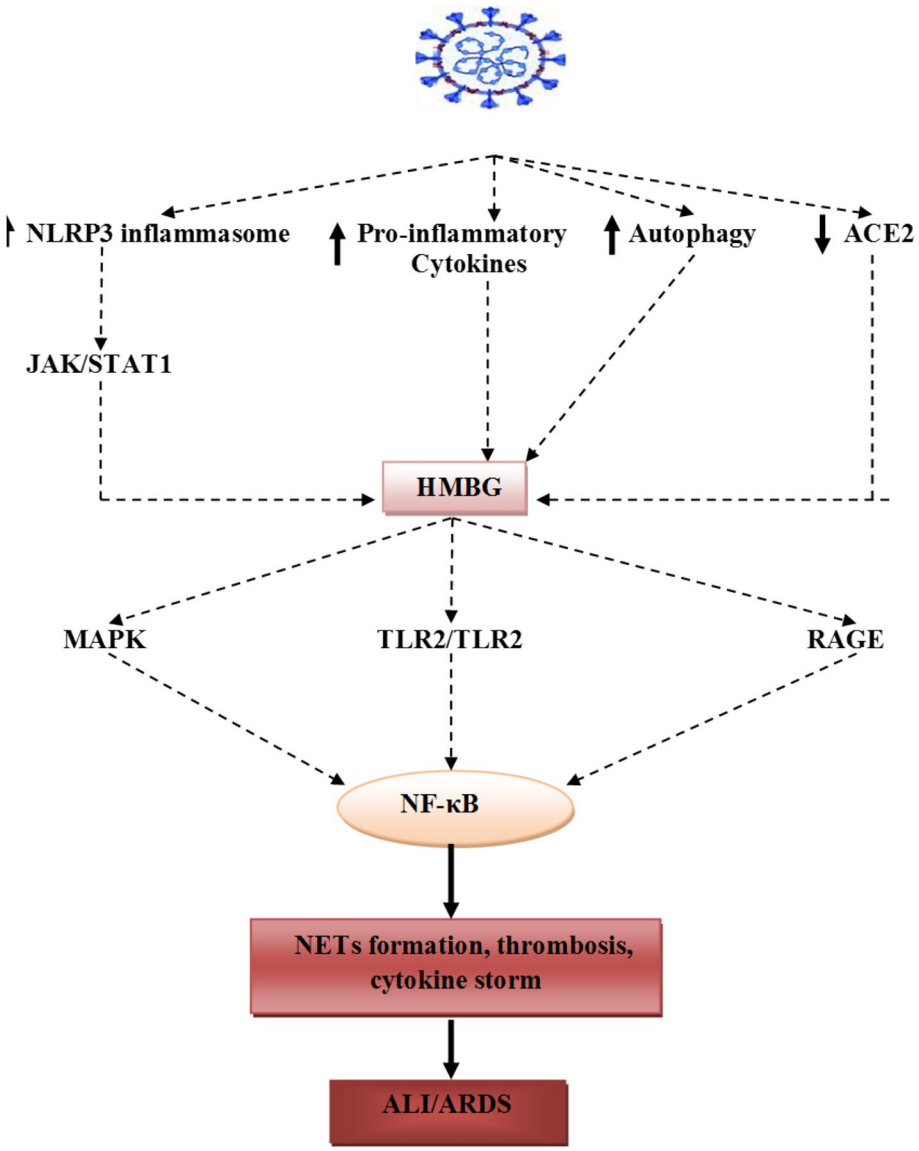

Fig. 2 SARS-CoV-2-induced ALI/ARDS: SARS-CoV-2 infection leads to activation release of extracellular high-mobility group box 1 (HMGB1) through down-regulation of ACE2, and activation of NLRP3 inflammasome, autophagy and TLR2/TLR4. HMGB1 activates TLR2, TLR4, RAGE receptors and mitogen-activated protein kinase (MAPK), provoke activation of NF-κB signaling pathway, which induces NETs formation, thrombosis and cytokine storm. These inflammatory mediators cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

due to in vitro direct antiviral activities, decreased the spread of the virus and reduction of viral load (Al-Kuraishy and Al-Gareeb 2020). Hydroxychloroquine has potent anti-inflammatory effects through various mechanisms; one of these is inhibition release of HMGB from activated immune cells through inhibition of PH-dependent lysosomotropic effects (Zhang et al. 2020). As well, hydroxychloroquine assuages NETs formation-induced HMGB release in SARS-CoV-2 infection (Roldan et al. 2020). Indeed, hydroxychloroquine blocks autophagy and prevents release of HMGB (Zeh et al. 2020). Jansen et al. (2021), reported that hydroxychloroquine blocked the endosomal TLR signaling, with subsequent prevention of interferon activation and HMGB release in SARS-CoV-2 infection.

Thrombomodulin

Thrombomodulin is an integral membrane protein expressed in different cells mainly endothelial cell, monocyte and dendritic cells, it converts thrombin into an anticoagulant enzyme (Loghmani and Conway 2018). Thrombomodulin blocks and degrades free extracellular HMGB with the aid of proteolytic action of thrombin. Thus, recombinant thrombomodulin is used in the management of coagulopathy and inflammatory reactions in sepsis (Vincent et al. 2019). In COVID-19 era, pulmonary endothelial cell injury-induced thrombosis in severe infection is mediated through inhibition in the release of thrombomodulin (O'Sullivan et al. 2020). Hultstrom et al. (2021) illustrated that high circulating inflammatory

angiopoitin-2 receptors in critical COVID-19 patients are associated thrombosis and development of ARDS through inhibition of thrombomodulin. Therefore, recombinant thrombomodulin might be effective in the management of COVID-19, through inhibition of HMGB-induced inflammation and thrombosis.

Haptoglobin

Haptoglobin is an acute-phase protein, binds free hemoglobin during intravascular hemolysis, and also inactivates extracellular HMGB at site of inflammation. Haptoglobin-HMGB1 complex activates macrophages for synthesis and release of anti-inflammatory IL-10, which, counteracted the action of excess pro-inflammatory cytokines during acute inflammatory conditions (Yang et al. 2017). However, in severe inflammatory process and when associated with bleeding at inflammatory site, the haptoglobin dissociated from HMGB-binding site, and attached free hemoglobin due to strong affinity of haptoglobin to the free hemoglobin (Devides et al. 2018). Therefore, inherited or acquired deficiency of haptoglobin is associated with exaggerated inflammatory reactions due to high unopposed free extracellular HMGB (Dahan et al. 2018). It has been observed that recombinant haptoglobin is effective in management of ALI, experimental pneumonia, trauma, and transfusion-mediated hemolysis (Remy et al. 2018). Therefore, recombinant haptoglobin therapy might be of interest in management of patients with severe COVID-19 due to its potential anti-inflammatory through blocking of HMGB-mediated thrombotic and inflammatory reactions.

Heparin and heparinoid compounds

Heparin is an anticoagulant agent, acts through activation of endogenous anti-thrombin III, has high affinity to the extracellular HMGB (Li et al. 2015). Binding of heparin to the HMGB, reduces the ability of HMGB to activate RAGE receptors on the activated macrophages (Rouhiainen et al. 2018). Therefore, heparin mitigates inflammatory reactions that are induced through HMGB/RAGE receptors axis. On the other hand, heparinoid, which is low molecular weight heparin (LMWH), has anti-inflammatory effect with very low anti-coagulant activity has been used successfully in management of ALI through inhibition of neutrophil-mediated release of HMGB (Rasmuson et al. 2019; Utsunomiya et al. 2018). Therefore, heparin and other LMWH derivatives are effective in management of critical COVID-19 patients their antiviral and anti-inflammatory effects (Hippensteel et al. 2020).

Resveratrol

Resveratrol is a phytomedicine containing phenol molecule that has a protective function when produced from plants under stressful conditions (Salehi et al. 2018). Different studies reported that resveratrol has potent anti-inflammatory effects through suppression of HMGB-mediated signaling pathway, such as expression of TLR4, NF-κB, MyD88, during acute inflammatory disorders (de Sá Coutinho et al. 2018). (de Oliveira et al. 2019) confirmed that resveratrol was effective against lipopolysaccharide (LPS)-induced ALI through amelioration of inflammatory signaling mediators. Thus, resveratrol might be probable therapy in management of patients with COVID-19 through suppression of SARS-CoV-2-induced cytokine storm and development of ALI/ARDS (Hoang 2020). Also, resveratrol has potent in vitro antagonistic action against SARS-CoV-2 viral replication.

Glycyrrhizin

Glycyrrhizin is an herbal medicine derived from licorice roots, widely used in Chinese traditional medicine, has potent anti-inflammatory activities through inhibition of HMGB-mediated signaling pathway (Paudel et al. 2020). In addition, glycyrrhizin suppressed the viral replication of SARS-CoV, flaviviruses and H5N1 influenza (Wang et al. 2015). Besides, glycyrrhizin attenuates LPS-induced ALI through inhibition release of HMGB1 and other inflammatory mediators in experimental studies (Qu et al. 2019b). Recently, different preclinical and clinical studies highlighted the potential role of glycyrrhizin in COVID-19 through modulation of SARS-CoV-2 infectivity. It inhibits SARS-CoV-2 binding to the ACE2, alters viral lipid membrane, decreases the production of airway exudates, combats the SARS-CoV-associated secondary bacterial infection, and attenuates cellular inflammatory signaling with suppression of macrophage activity (Luo et al. 2020a; Gomaa and Abdel-Wadood 2021).

Dexmedetomidine and ketamine

Dexmedetomidine is an anxiolytic and sedative drug with sympatholytic effect, acts through activation of α-2 presynaptic adrenoceptor (Weerink et al. 2017). Also, dexmedetomidine inhibits release of pro-inflammatory cytokines via stimulation of cholinergic nicotinic receptor type 7 (7nAChR) (Xiang et al. 2014). It has been shown that dexmedetomidine attenuates LPS-induced ALI through inhibition of lung HMGB1-mediated TLR4/Nf-kB axis (Meng et al. 2018). Therefore, dexmedetomidine may reduce COVID-19 severity through different pathways including, inhibition of TLR4, release of HMGB1, NLRP3 inflammasome, NF-κB signaling and JAK/STAT signaling (Jain et al.

2021). Other 7nAChR agonists also have pulmo-protective effects through inhibition of lung macrophages and release of pro-inflammatory cytokines during SARS-CoV-2 infection (Jain et al. 2021). Dexmedetomidine is commonly used in combination with ketamine during anesthesia and ventilation support during mechanical ventilation (Luscri and Tobias 2006). Ketamine also inhibits release of HMGB1 and NETs formation during ALI (Akinosoglou et al. 2020). Further, ketamine has been shown to attenuate sepsis-induced ALI by down-regulating the HMGB1-RAGE pathway (Zhang et al. 2018). It was reported that ketamine protected against lung injury via down-regulation of the expressions of HMGB1 and TLR4 as well as the activity of myeloperoxidase in the inflamed lungs (Qin et al. 2015). Thereby, due to their potent anti-inflammatory effects, both ketamine and dexmedetomidine are more appropriate anesthetic agents in the management of ARDS in COVID-19 patients.

Metformin

Metformin is an insulin-sensitizing agent, used as first-line therapy in management of type 2 diabetes mellitus (T2DM) (Al-Kuraishy et al. 2020d; Al-Brakati et al. 2020; Othman et al. 2021b). Metformin has potent anti-inflammatory effect through activation of adenosine monophosphate protein kinase (AMPK) and inhibition of HMGB1 release (Al-Kuraishy et al. 2020d). Horiuchi et al. (2017) revealed that metformin directly inhibits HMGB1 acidic terminal part released from damaged cells in acute liver injury. Metformin therapy is associated with better clinical outcomes and low mortality in COVID-19 patients (Luo et al. 2020b). The case–control study of Al-Kuraishy et al. (2021a) illustrated that metformin therapy in COVID-19 patients with T2DM is linked with reduction of ALI and ischemic stroke, due to its potent anti-inflammatory effects.

Finally, this perspective highlighted the potential role of HMGB1 in the pathogenesis of SARS-CoV-2 infections and associated inflammatory reactions-induced-ALI/ARDS. Therefore, targeting of HMGB1 signaling pathway might be a new therapeutic modality in the management of COVID-19.

Salicylic acid

Salicylic acid (SA) is an organic compound, has antibacterial and antiseptic activity, used mainly in treatment of dermatological disorders like psoriasis, acne, and seborrheic dermatitis (Arif 2015). It has been reported that SA had ability to blocks the pro-inflammatory effect of HMGB1 at lower micromolar concentration to block the enzyme activity of COX-1 and COX-2 (Klessig et al. 2016). Of note, HMGB1 induces expression of COX-2 and other cytokine genes with propagation of inflammatory changes (Park et al. 2018). SA unlike acetylsalicylic acid (aspirin) which inhibits activity of COX-2, inhibits synthesis of COX-2 (Klessig et al. 2016; Othman et al. 2021a). Therefore, SA derivatives like acetylsalicylic acid could be effective in the management of COVID-19 by inhibiting HMGB1 and other inflammatory signaling pathways like NF-κB (Cacciapuoti and Cacciapuoti 2021). A cohort study involved 984 COVID-19 patients according to the use of acetylsalicylic acid before hospitalization, showed that COVID-19 patients with acetylsalicylic acid treatment had high survival rates compared to the non-user (Sisinni et al. 2021). These observations suggest the protective role acetylsalicylic acid against COVID-19 severity by reducing platelet activation and thrombotic complications.

Conclusion

HMGB1 signaling pathway has a noteworthy role in the pathogenesis of SARS-CoV-2 infections and linked with development of ALI and ARDS in COVID-19 patients. Different endogenous and exogenous agents may affect release and activation of HMGB1 pathway. Targeting of HMGB1-mediated TLR2/TLR4, RAGE and MAPK signaling, might be a new supporting line against development of ALI and/or ARDS in severely affected COVID-19 patients. Prospective and clinical trial studies are merited and reasonable to confirm the therapeutic benefit of anti-HMGB1 in managing of COVID-19.

Funding No funding.

Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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