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High mobility group box 1 (HMGB1) in COVID-19

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Key point

In COVID-19, extracellular high mobility group box1 (HMGB1) is released from monocytes, macrophages, and dendritic cells and enhance inflammatory reactions.

Keywords: COVID-19, HMGB1, Damage-associated molecular pattern

Coronaviruses have caused two global health threats: severe acute respiratory syndrome and Middle East respiratory syndrome, and the present COVID-19 that emerged from China. This virus's source is zoonotic and spreads by cough, sneeze, contaminated hand and generally transmitted through direct contact. Hyper-production of cytokines (cytokine storm or cytokine release syndrome) leads to symptomatic phase manifestations, such as fever, myalgia, cough, multi-organ failure, and alveolar injury that reduce airway capacity, followed by severe respiratory failure (1,2).

Both mild and severe forms of the disease occur following leukocyte release of cytokines, such as interleukin (IL)-6, IL-1β, IL-10, TNF, GM-CSF, IP-10 (IFN-induced protein 10), IL-17, MCP-3, and IL-1, which circulate ln blood. Supportive therapy along with mechanical ventilation are utilized in severe cases. So far, preventive methods have been proved to be the best strategy against COVID-19, and future understanding of viral pathophysiology is crucial for producing the best Treatment and vaccine (3,4).

High mobility group box 1

High mobility group box 1 (HMGB1), as an abundant nuclear and cytoplasmic protein present in mammalian cells, has intracellular and extracellular roles. The intracellular role is binding to DNA to stabilize nucleosome structure and regulate gene transcription. In addition to intracellular roles, it plays many functions outside of cells (5). Extracellular HMGB1 is released from monocytes, macrophages, and dendritic cells to enhance inflammatory reactions (6).

Secretion of HMGB1 has been involved in the pathogenesis of several disorders, including sepsis, viral infections, arthritis, cancer, autoimmunity, and diabetes. It has been suggested that in inflammatory conditions, HMGB1 could be a proper therapeutic target (7).

HMGB1, as a damage-associated molecular pattern (DAMP), signals for advanced glycation end-products (RAGE), Toll-like receptor 2 (TLR2), and Toll-like receptor 4 (TLR4) to stimulate inflammatory cells to release pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), IL-1, and IL-6 (Figure 1) (7). AGER gene encodes a cell surface transmembrane multi-ligand receptor, which is named Receptor advanced glycation end-products (RAGE). RAGE mainly is expressed in the lung. After HMGB1 attached to the RAGE, multiple pathways (such as NFκB, Akt, p38, and MAP kinases) happen that began an unfavorable pro-inflammatory state. RAGE receptor may indicate the severity of the disease-related viral infection and may act as a potential mediator for inflammatory disease during SARS-CoV-2 (8).

Functional role HMGB1/TLR4-mediated neuro-inflammation has been demonstrated

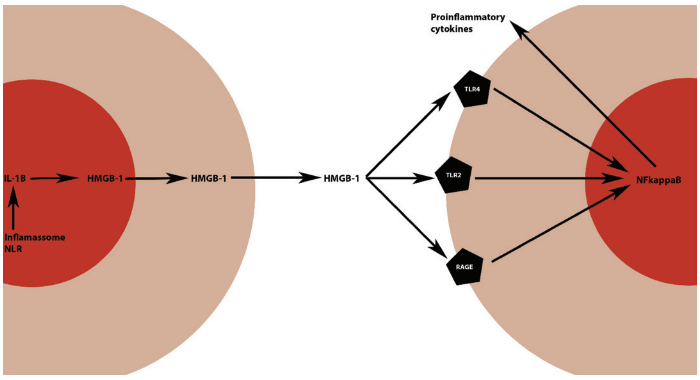

Figure 1. Functional association between HMGB-1 and inflammasome. NLR (nucleotide-binding oligomerization domain-like receptor) is a complex of proteins that release IL-1B. IL-1B induces the HMGB-1 nuclear translocation to cytoplasmic. Exogenous HMGB-1 can act via receptors (RAGE, TLR2 and TLR4) to stimulate NF-kappa B, release pro-inflammatory cytokines, and elicit injurious inflammatory responses.

in brain disease, explaining some Neuro-inflammation signs and symptoms of COVID-19 such as fever, loss of smell, taste, and appetite. Interaction between HMGB1 via TLR4 expression on neurons, microglial cells, and astrocytes induces substantial pro-inflammatory cytokine production (4).

Subsequently, systemic inflammatory responses include acute lung injury, epithelial barrier dysfunction, ischemic injury in the heart, liver, brain, and death happening by HMGB1(4,9).

HMGB1 in COVID-19

ACE2 (angiotensin-converting enzyme 2), a transmembrane protein that is essential for the entry of SARS-COV-2 into target cells. After viral spike (S) proteins bind to cellular receptors on lung and intestinal cells, sudden acute respiratory syndrome (SARS) may happen (6).

ACE2 activation increases the upregulation of HMGB1 in cells and grows downstream pro-inflammatory cascades. Increasing production of HMGB1 by cellular injury and frustration of secreted HMGB1 poses Ang II-induced hyper-permeability endothelial.

The major cause of lung injury and mortality in many severe pulmonary inflammatory conditions, including COVID-19, is excessive host inflammatory response. RAGE is mainly expressed in the lungs to face large amounts of extracellular HMGB1 in necrotic respiratory epithelial cells (4,8,10,11).

Even now, there are no adequate and approved therapies for outfacing inflammatory mediators in COVID-19. There are several methods for controlling the production, secretion, and neutralization of HMGB-1 and, consequently, the inflammatory process (7,9).

Group 1; is associated with using anti-HMGB-1 antibodies treatment with neutralizing anti-HMGB-1 monoclonal or polyclonal antibody group 2; inhibition of HMGB-1 releases from the nucleus into the extracellular such as guanylhydrazone containing compounds, cholinesterase, PKC inhibitor, double-stranded nucleic acid or nucleic acid analog molecules, tanshinones and ethyl-pyruvate also ACE inhibitors and angiotensin receptor blockers could reduce the secretion of HMGB1. These experiments would be consistent with possible interactions between HMGB1 and the renin-angiotensin system.

Group 3; HMGB-A box as a competitive antagonist of HMGB-1.

Group 4; blockage of RAGE-HMGB-1 signaling using RAGE antagonists such as an antibody to RAGE or an antigen-binding fragment, a soluble polypeptide, and a RAGE small molecule antagonist.

Group 5; blockage of TLR-HMGB-1 signaling using anti-TLR2 antibodies or an antigen-binding fragment or a soluble TLR2 polypeptide blocking HMGB-1-TLR interaction.

Group 6; other molecules that modulate HMGB-1 activity, such as thrombomodulin.

Authors' contribution

FK and AP prepared the first draft. AB and ZM edited the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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