Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Pharmacological targeting of HMGB-1 translocation: A potential therapeutic strategy for COVID-19

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I read the paper by Li et al. [1] with great interest. In their study, the authors demonstrated that liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, was able to inhibit nucleus-to-cytoplasm translocation of high-mobility group box 1 protein (HMGB-1), leading to protection against lethal renal ischemia-reperfusion injury (IRI). This points to the fact that subcellular translocation of HMGB1 could contribute to the pathogenesis of different human diseases such as infections. Although most studies highlighted the importance of extracellular HMGB1 in the pathogenesis of viral infections, recent data suggest that intracellular HMGB1 may be considered as a target for the development of novel antiviral drugs.

Discovering new pharmacological targets is of vital importance for the development of effective drugs against emerging infectious diseases, including coronavirus disease 2019 (COVID-19). Herein, I discuss the potential of targeting cellular translocation of HMGB-1 as a therapeutic strategy to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In addition to the extracellular activities of HMGB1, nuclear HMGB1 could potentially be involved in the antiviral responses in COVID-19.

The receptor for advanced glycation end products (RAGE) interacts with several ligands such as HMGB1 and S100/calgranulins (e.g., S100A12) released from infected cells. RAGE activation induces the NF-κβ-mediated expression of proinflammatory genes, including inflammatory cytokines and cell adhesion molecules [2]. The pathogenic role of extracellular HMGB1 in COVID-19 has been investigated in order to evaluate its therapeutic potential [3]. They showed that recombinant human HMGB1 (rhHMGB1) was able to induce the expression of ACE2 (angiotensin-converting enzyme 2), the main receptor for SARS-CoV-2, in human lung epithelial cells through RAGE signaling.

Unlike the extracellular HMGB1, its intracellular activities have not been studied in SARS-CoV-2 infection. However, a few studies have examined the role of nuclear HMGB1 in viral infections such as Zika virus (ZIKV) and dengue virus (DENV) infections. Resveratrol (RESV) has been demonstrated to exert antiviral activity against DENV by inhibiting HMGB1 translocation from the nucleus to the cytoplasm, resulting in HMGB1 accumulation in the nucleus. Consequently, nuclear HMGB1 was shown to enhance the expression of interferon-stimulated genes (ISGs) through interaction with their promoters. As a result, RESV can suppress DENV replication by blocking nucleocytoplasmic HMGB1 translocation [4]. Based on the fact that RESV has the ability to inhibit the replication of SARS-CoV-2, the inhibition of HMGB1 translocation may be a mechanism of its antiviral activity. A recent study revealed that ZIKV infection promotes HMGB1 translocation from the nucleus to the cytoplasm [5]. Treatment of ZIKV-infected Huh7 cells with dexamethasone reduced ZIKV replication. It is noteworthy that the mechanism by which dexamethasone exerts its antiviral activity against ZIKV is mediated by inhibition of HMGB1 translocation. Due to its anti-inflammatory and immunosuppressive effects, dexamethasone is the first drug reported to save the lives of patients with COVID-19 disease. Therefore, HMGB1 intracellular translocation might play a crucial role in dexamethasone's antiviral action against SARS-CoV-2 infection. The mechanism of HMGB1 translocation from the nucleus to the cytoplasm has been studied using pharmacological inhibition of JAK/STAT1 [6]. The study discovered that JAK/STAT1 pathway mediates HMGB1 nuclear translocation. The results suggest that targeting JAK/STAT1 pathway could be a potential therapeutic strategy to reduce HMGB1 release.

Taken together, HMGB1 expression in lung, including epithelial cells and alveolar macrophages make it an attractive therapeutic target for viral respiratory infections such as COVID-19. Nuclear HMGB1 appears to have antiviral effects and inhibit viral replication. In fact, antiviral activity of some anti-COVID-19 agents (e.g., resveratrol and dexamethasone) is mediated through inhibiting translocation of nuclear HMGB1 to the cytoplasm (Fig. 1). Thus, pharmacological targeting of HMGB1 nucleus-to-cytoplasm translocation may represent a feasible therapeutic approach to SARS-CoV-2 infection. Future research is needed to carefully examine this potential therapeutic target, particularly in the context of viral infections.

Declaration of Competing Interest

The author(s) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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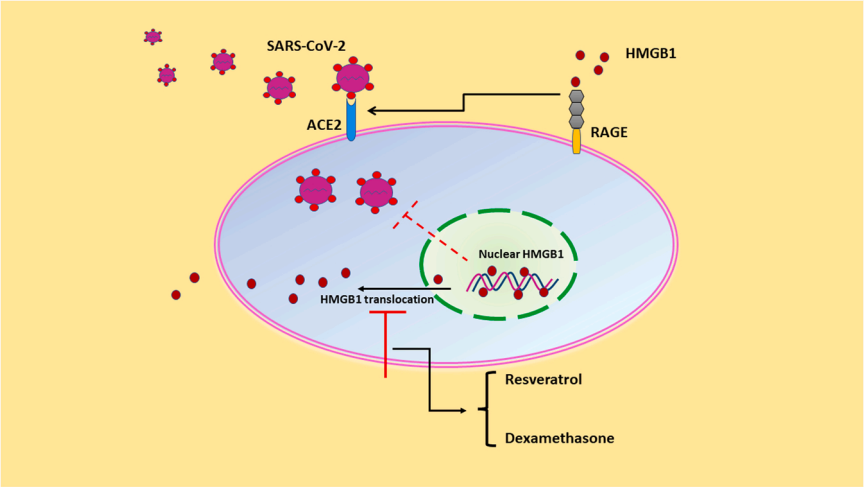

Fig. 1. HMGB1 translocation as potential pharmacological target in human lung cells infected with SARS-CoV-2. HMGB1 induces the expression of ACE2 through RAGE activation. Resveratrol and dexamethasone exert antiviral activity by inhibiting HMGB1 translocation from the nucleus to the cytoplasm, resulting in HMGB1 accumulation in the nucleus. HMGB1 retained in the nucleus suppresses viral replication by upregulating the expression of interferon-stimulated genes (ISGs).

Data Availability

No data was used for the research described in the article.

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