Commentary

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr
DOI: 10.1159/000508291

Received: April 23, 2020
Accepted: April 28, 2020
Published online: May 6, 2020

HMGB1: A Possible Crucial Therapeutic Target for COVID-19?

Maria Elisabeth Street

Division of Paediatric Endocrinology and Diabetology and Research Laboratory, Department of Mother and Child, Paediatrics, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

Since COVID-19 is a global health emergency, any hypothesis that can explain the course and complications of this disease, and lead to a more focused treatment and self-limiting progression of the infection, should be put forward. A whole series of symptoms and features related to this disease have emerged from reports including fever, cough, myalgia, sore throat, dyspnea, headache, lymphopenia, and acute respiratory distress syndrome (ARDS), but also acute cardiac and kidney injury, secondary infection, shock [1], vasculitis, thrombosis, and disseminated intravascular coagulation. In some patients, significant levels of antiphospholipid antibodies have been found [2], which, in association with extremely elevated proinflammatory cytokines, are probably responsible for the worst course and outcome, and have led to the current ongoing trials on biological drugs against IL-1 receptor, IL-6, and IL-6 receptor, among others [3]. Fibrosis is present in the lungs of severely affected patients [4]. Amyloidosis and thrombosis have been reported by colleagues as present in autoptic specimens but have not yet been reported in the literature.

Patients with obesity are at an increased risk of developing COVID-19 [5, 6], possibly aggravated further by the presence of nonalcoholic fatty liver disease [6]. Obesity is also characterized by low-grade chronic inflammation.

High mobility group box-1 (HMGB1) is a chromatin-linked, nonhistomic, small protein with cytokine activity that has nuclear, cytosolic, and extracellular actions. It binds to chromosomal DNA but also to Toll-like receptor 3 (TLR3), TLR4, and the receptor for advanced glycation end products (RAGE) that activates nuclear factor (NF)-κB (Fig. 1a), which mediate the upregulation of leukocyte adhesion molecules as well as the production of proinflammatory cytokines and angiogenic factors that promote inflammation. HMGB1 was initially known as alarmin and is a well-recognized damage-associated molecular pattern (DAMP) protein.

HMGB1 has been extensively studied within the field of endocrinology as it is clearly involved with obesity [7], insulin resistance, and diabetes [8], and more recently polycystic ovary disease [9], another condition characterized by low-grade chronic inflammation (Fig. 1b).

Interestingly, it has been recognized that HMGB1 regulates autophagy [10] and could potentially be a biomarker of acute lung injury [11]. Autophagy is one of the mechanisms involved in COVID-19 and is involved in viral entry and replication in cells, so targeting this pro-

karger@karger.com
www.karger.com/hrp

Maria E. Street, MD, PhD
Division of Paediatric Endocrinology and Diabetology and Research Laboratory
Department of Mother and Child, Paediatrics
AUSL-IRCCS di Reggio Emilia, Viale Risorgimento 80, IT–42123 Reggio Emilia (Italy)
mariaelisabeth.street@ausl.re.it

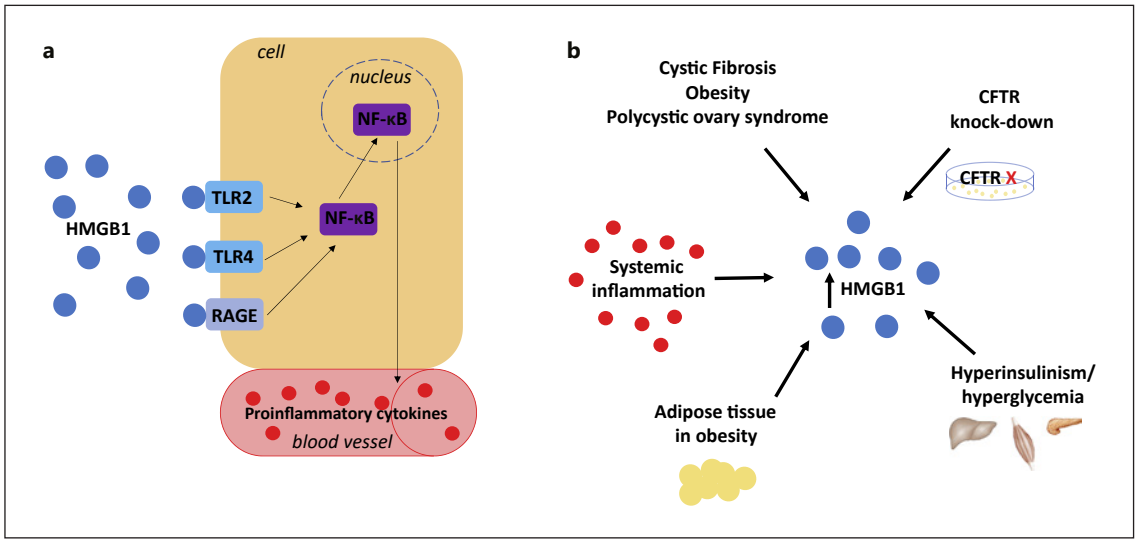

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Fig. 1. a HMGB1 shows both intracellular and extracellular effects. By binding to TLR2, TLR4, and RAGE, it activates NF-κB which leads to the production of proinflammatory cytokines that have local and systemic effects. **b** HMGB1 is increased both locally and in the circulation in conditions like obesity, cystic fibrosis, and polycystic ovary, and, whenever insulin resistance occurs, it is produced by adipose tissue and the immune system. CFTR malfunction causes an increase in HMGB1, besides other changes such as inflammation and increased autophagy.

cess has been suggested as a possible novel therapeutic strategy for COVID-19 [12].

Furthermore, HMGB1 expression is increased in thrombosis-related diseases [13, 14], and has been studied in alveolar epithelial cells [14]. Finally, HMGB1, via RAGE, mediates sepsis-triggered amyloid-β accumulation in diseases of the central nervous system associated with impaired cognitive function, e.g., neurodegenerative diseases [15].

Most interestingly, *HMGB1* gene polymorphisms are associated with hypertension in the Han Chinese population [16], which also suggests that it could be implicated in the outcome and course of COVID-19 in some individuals.

It is now well known that SARS-CoV2 requires angiotensin-converting enzyme (ACE) II receptors for viral entry and replication [17]. Kuba et al. [18] showed in mice that SARS-CoV downregulated ACE II protein, contributing to severe lung injury. Interestingly, ACE II overexpression has been reported to reduce HMGB1, besides reducing apoptosis in the myocardium postinfarction, in a rat model [19]. This leads to the hypothesis that a reduction in ACE II induced by the virus would in turn increase HMGB1, thus contributing to the "cytokine storm" and the worst scenarios seen with COVID-19 infection.

The inflammasome mediates HMGB1 translocation from the nucleus to the cytoplasm, with subsequent release from the cell via type 1 interferon JAK/STAT1 activation. Thus, pharmacological inhibition of JAK/STAT1 could be an approach for reducing circulating HMGB1 [20]. HMGB1 is recognized as a drug target, in particular for the salicylic acid (SA) derivatives 3-aminoethyl SA and amorfrutin B1, and methotrexate, inflachromene, and glycyrrhizin have also been shown to lower HMGB1 [21]. In 2003, in an in vitro model, a German group used glycyrrhizin to inhibit the replication of SARS-CoV1, the virus that was circulating at that time, and described this compound as effective as ribavirin and mycophenolic acid, and more effective than 6-azauridine and pyrazofurin. This finding was confirmed in vitro using serum samples from patients, but the mechanism of action remained unclear [22].

In addition to these considerations, in 2004, it was hypothesized that HMGB1 could play a possible pathogenic role in SARS-Cov1 [23].

Finally, my research group previously showed that cystic fibrosis transductance regulator (CFTR) malfunction, as found in cystic fibrosis, increases HMGB1 serum concentrations, along with inflammation, and further increases are observed at the onset of the specifically related diabetes [24]. This suggests that changes in CFTR expres-

sion and/or specific polymorphisms could play a role, particularly in the lung, and some of the new CFTR modulators should be considered for treatment if this were indeed the case [25, 26]. Furthermore, diabetes is a recognized risk factor for Sars-CoV2 infection [27], and HMGB1 is known to be increased in diabetes [8].

In conclusion, I support the need for assaying HMGB1 in the serum samples of COVID-19 patients who have been affected differently and are thus currently receiving different treatment. This would clarify whether HMGB1 could be a marker of poor prognosis and a potential target for treatment. Furthermore, could the *HMGB1* gene polymorphisms explain some of the variations observed in these patients? If so, this should be addressed and integrated into treatment.

Should we now be considering add-on treatment with drugs like glycyrrhizin, that reduce HMGB1, and then rapidly hypothesize the dose and mode of administration?

Disclosure Statement

I declare there are no competing interests.

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