LETTER TO THE EDITOR-IN-CHIEF

High mobility group box 1 (HMGB 1): a new protein in the pathogenesis of ENT inflammatory and infectious diseases

HMGB 1 una nuova proteina nella patogenesi della patologia infiammatoria ed infettiva ORL

D. PASSALI, E. KERN[1], R. LEI CHEN[2], L. BELLUSSI

University of Siena, Italy; [1] Gromo Institute-University of Buffalo, NY; [2] The People's Liberation Army (PLA) Genaral Hospital, Beijing, China

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In addition to the well-known components of the immune response to inflammation, other inflammatory pathways have been recently invoked. Among these, an inflammatory molecule called high mobility group box 1 (HMGB1) can be highlighted, which is an evolutionary ancient protein that serves predominately as a DNA-binding protein with "alarmin" activity. Yang et al. [1] used the term "alarmin" to indicate numerous granule-derived mediators that rapidly galvanize antigen-presenting cells (APCs) and trigger innate and adaptive immune responses. They represent the first host response to exogenous (infections) and endogenous (injuries) danger signals. Alarmins have the dual capacity to recruit and activate inflammatory cells including dendritic cells (DCs), using Giα-protein-coupled receptor(s) (GiPCR) and activating receptor(s), respectively. Alarmins are usually constitutively present in cells, such as leukocytes and epithelial cells, as components of the granules, cytoplasm and nucleus. They are endogenous peptides that are released in host defence against danger signals, and therefore, can be considered as a subset of damage associated molecular patterns (DAMPs) [1]. HMGB1 is ubiquitously expressed in the nuclear compartment of eukaryotic cells functioning as a transcriptional regulator via interaction of its A-box and B-box subunits with DNA. Therefore, quiescent macrophages/monocytes constitutively express HMGB1 and maintain an intracellular "pool" of HMGB1 predominantly in the nucleus. In the late 1990's, Wang et al. [2] reported that extracellular HMGB1 is actively released as a late mediator of inflammation in sepsis by activated macrophages/monocytes. After stimulation with exogenous bacterial products such as endotoxin, or with endogenous pro-inflammatory cytokines such as TNF-α, IL-1β and IFN-γ, cultures of macrophages, monocytes, and pituicytes actively release HMGB1 in a time- and dose-dependent manner. In addition to its active release, HMGB1 can also be released passively from necrotic or damaged cells. However, HMGB1 is not released by apoptotic cells, which degrade without setting off an inflammatory response. Therefore, HMGB1 is extracellularly released as a result of loss of membrane integrity upon necrosis of nucleated cells (including neutrophils) and by activated leukocytes via an initial acetylation on many of the 43 lysine residues of HMGB1 in the nucleus. As an extracellular protein, HMGB1 has pleomorphic effects including activation of NF-κB, diffuse endothelial activation, hepatocellulary injury, epithelial leak, and systemic activation of inflammatory cells [3]. HMGB1 activates inflammatory cells through interactions between the receptor for advanced glycation end-products (RAGE) or toll-like receptor (TLR)-2 and -4. This occurs through the coordinated release from stimulated cells following acetylation of nuclear HMGB1, leading to cytoplasmic translocation and export via secretory vesicles. Once released, HMGB1 has been reported to have pro-inflammatory effects, and high levels have been associated with human or experimental models of sepsis [2], haemorrhagic shock, rheumatoid arthritis [4], systemic lupus erythematosus [5] and within the airways during ventilator-induced lung injury [6]. Recently [7], HMGB1 has been studied for its potential impact in cystic fibrosis lung disease.

Extracellular HMGB1 binds to cell surface receptors such as RAGE, TLR-2 and TLR-4, and possibly to yet unknown receptors. Receptor binding leads to activation of the transcription factors NF-κB, inducing transcription of multiple pro-inflammatory genes. Upon (co-)activation with HMGB1, macrophages produce pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, macrophage inflammatory protein-1α and MIP-2β [8].

HMGB1 acts as an alarmin because it induces both migration and activation of DCs and enhances antigen-specific immune responses that favour Th1 polarization [9]. This

protein is chemotactic for immature DCs and can contribute directly to local recruitment of DCs.
Numerous studies have shown the participation of alarmins such as HMGB1 in the development of inflammation and the immune response. The levels of neutrophil-derived alarmins are high under many inflammatory conditions, whereas blockade of some of these mediators have been shown to ameliorate the manifestations of acute inflammatory reactions. There is increasing evidence that HMGB1 contributes to the pathogenesis of chronic inflammatory and autoimmune disease due to its pro-inflammatory and immunostimulatory properties. Intratracheal administration of HMGB1 induces lung neutrophil infiltration, local production of pro-inflammatory cytokines and acute lung injury [10]. After viral infection, HMGB1 may be actively or passively released by infected cells producing an inflammatory response driven both by infected cells and neighbouring innate immune cells. HMGB1 released by tumour tissues might contribute to tumour progression related to pro-inflammatory and pro-angiogenetic effects.
The recent discovery of HMGB1 as a critical mediator of inflammation has stimulated an increasing interest in the field of inflammation research. These important new findings have also suggested different perspectives in the ENT field where further investigation is needed to identify possible new therapies for viral/bacterial infection and other inflammatory diseases of the upper airways.
Our research group, in collaboration with the "ENT Gromo Institute" in Buffalo (USA) and the "Tongren General Hospital" of Beijing (China), is examining the results of a research projected to offer a quantitative evaluation of this protein observed in the mucosa of patients suffering from allergic and vasomotor rhinitis, rhinosinusitis and nasal polyposis.
In light of the more recent knowledge and technologies, this study has been structured following specific methodologies.
Moreover, the possible application of certain substances capable of inhibiting the pro-inflammatory effects of HMGB1 is also under investigation. The anti-inflammatory and immunosuppressive effects could be obtained through three main mechanisms: inhibiting the release; blocking protein receptors (RAGE, TLR2, TLR4 and TLR9) through direct receptor antagonism; or inactivating HMGB1 protein after its release from the necrotic cells through a scavenger mechanism.
These studies were projected according to two main lines of research: the first is aimed to define a suitable qualitative and quantitative determination methodology. In this view, two main methodological approaches should be considered: 1) immunohistochemical staining for HMGB1 and other inflammatory cytokines (TNF-α, IL-1βF) followed by a semiquantitative analysis of cells staining positive for the protein of interest; 2) immunofluorescence staining and confocal analysis of intra/extracellular distribution of the HMGB1 protein.
The second research line has the aim of better understanding the mechanism of action of substances involved in reduced levels of the protein and to determine their clinical relevance, compliance, cost/benefit ratio and safety profile.
It seems important to suggest that clinical and experimental researches on these topics should be continued, with the aim of reducing issues due to diseases which are pertinence to the ENT field, and which are now recognized as "Social Diseases"

References

1 Yang D, de la Rosa G, Tewary P, et al. *Alarmins link neutrophils and dendritic cells*. Trends Immunol 2009;30:531-7.

2 Wang H, Bloom O, Zhang M, et al. *HMG-1 as a late mediator of endotoxin lethality in mice*. Science 1999;285:248-51.

3 Lotze MT, Tracey KJ. *High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal*. Nat Rev Immunol 2005;5:331-42.

4 Kokkola R, Sundberg E, Ulfgren AK, et al. *High mobility group box chromosomal protein 1: a novel proinflammatory mediator in synovitis*. Arthritis Rheum 2002;46:2598-603.

5 Jiang W, Pisetsky DS. *Expression of high mobility group protein 1 in the sera of patients and mice with systemic lupus erythematosus*. Ann Rhem Dis 2008;67:727-8.

6 Ogawa EN, Ishizaka A, Tasaka S, et al. *Contribution of high-mobility group box-1 to the development of ventilator-induced lung injury*. Am J Respir Crit Care Med 2006;174:400-7.

7 Gaggar A, Rowe SM, Hardision M, et al *Proline-Glycine-Prolyne (PGP) and High Mobility Group Box Protein-1 (HMGB1): potential mediators of cystic fibrosis airway inflammation*. Respir Med J 2010;4:32-8.

8 Voll RE, Urbonaviciute V, Herrmann M, et al. *High mobility group box 1 in the pathogenesis of inflammatory and autoimmune diseases*. Isr Med Assoc J 2008;10:26-8.

9 Urbonaviciute V, Fürnrohr BG, Meister S, et al. *Induction of inflammatory and immune responses by HMGB1-nucleosome complexes: implications for the pathogenesis of SLE*. J Exp Med 2008;205:3007-18.

10 Lin X, Yang H, Sakuragi T et al. *Alpha-chemokine receptor blockade reduces high mobility group box 1 protein-induced lung inflammation and injury and improves survival in sepsis*. Am J Physiol Lung Cell Mol Physiol 2005;289:583-90.

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Address for correspondence: Prof. Desiderio Passali, via Anagnina 718, 00118 Roma, Italy. E-mail: d.passali@virgilio.it