The Cytokine Activity of HMGB1 - Extracellular Escape of the Nuclear Protein

Nian-Kang Sun¹,², PhD; Chuck C.-K. Chao¹, PhD

High mobility group box 1 (HMGB1), a mobile chromatin protein, passively leaks from necrotic cells and signals neighboring cells that tissue damage has occurred. Resting, non-activated inflammatory cells such as monocytes or macrophages contain HMGB1 in the nuclear compartment. When activated by lipopolysaccharide or inflammatory cytokines, they actively translocate the nuclear HMGB1 into the cytoplasm; HMGB1 is then exocytosed. At least one receptor for extracellular HMGB1 has been identified. HMGB1 acts as a mediator of systemic inflammation; it causes different cells to divide, migrate or elicit an immune response. Here, we give an abridged review of the cytokine activity of HMGB1, including its secretion mechanism, the putative signal transduction pathways, and its role in several inflammatory diseases. Finally, we cite a few examples in which therapeutic administration of HMGB1 antagonists rescued mice from lethal sepsis, arthritis and liver damage. The new findings of HMGB1 as a cytokine provide a better understanding of inflammatory diseases, establishing a clinically relevant therapeutic target that is significantly more efficient than other known cytokines. (Chang Gung Med J 2005;28:673-82)

Key words: arthritis, cytokine, HMGB1, inflammation, sepsis.

1. Introduction

Mammalian HMGB1, formerly named HMG1 but also known as amphoterin and sulfoglucuronyl carbohydrate binding protein, SBP-1, was identified over 30 years ago. HMGB1 has turned out to be an abundant and ubiquitous component of chromatin. It binds preferentially to cruciform DNA, a non-double helix form of DNA. It also bends DNA, making it pliable to the assembly of multiprotein complexes, including many transcription factors. HMGB1-like proteins are also found in yeast, bacteria, and plants.

HMGB1 has been studied for a long time, but researchers have only recently started to understand its biological functions. As a well known chromatin architectural factor, it facilitates the assembly of site-specific DNA binding proteins to their cognate binding sites within chromatin. Besides this intranuclear function, it also has an extracellular function. This has led to the emergence of a new field in immunology that is focused on understanding the mechanisms of HMGB1 release, its biological activities and its pathological effects in sepsis, arthritis, cancer and other diseases. This review will primarily focus on HMGB1 as proinflammatory mediator and examples of HMGB1 as a therapeutic target in both acute and...
chronic inflammatory diseases, particularly in the settings of sepsis and arthritis which are now in preclinical development for planned clinical trials.

2. HMGB1 Basics

HMGB1 is a small protein (215 amino acids) and is a highly conserved non-histone DNA-binding protein between species. Structurally, HMGB1 is composed of three domains: two homologous DNA-binding motifs, A-box and B-box (called HMG boxes) that form an L-shaped structure and an acidic carboxyl terminus. A cytokine-inducing domain has been determined to be the first 20 amino acids of the B-box (Fig. 1). The human HMGB1 gene is located on chromosome 13q12. Multiple genes or pseudogenes within the genome have been suggested as Southern blot analysis of human genomic DNA has revealed several bands.\(^{(9-11)}\)

2.1 Major sites of expression

HMGB1 is highly conserved among species, with over 98% sequence identity between rodents and humans.\(^{(12-14)}\) HMGB1 is a ubiquitous protein and is widely distributed in all mammalian tissues. The site of expression of HMGB1 is tissue-specific with high levels found in the thymus, lymphoid tissue, testis, and neonatal liver.\(^{(15,16)}\)

During early development, HMGB1 protein is present in a subset of brain cells, with a very complex temporal, spatial and subcellular expression pattern. HMGB1 is nuclearily expressed in scattered cells apparently moving from the ventricular zone to the cortical plate. HMGB1 expression is strongly down-regulated at later developmental stages. In adult mouse brain, HMGB1 is undetectable in most cells and significant expression is maintained only in areas of continuing neurogenesis.\(^{(17)}\) HMGB1 plays a role in potentiating transcription. It is possible that the genes involved in cell growth control or maintenance of the un-differentiated state are especially dependent on HMGB1 for their expression. Whether HMGB1 is required in growing or un-differentiating cells remains to be elucidated.

2.2 Extracellular localization of HMGB1

Acetylation within the HMG-boxes is functionally important and influences the avidity of chromatin association and shuttling between the nucleus and cytoplasm. Acetylation of HMGB1 on certain lysine residues promotes the relocation from the nucleus to the cytoplasm and prevents its nuclear reentry, which is a prerequisite for extracellular secretion.\(^{(6,18)}\)

It has been known for several years that the HMGB1 protein is located on the external side of the cell membrane of neuronal cells.\(^{(19)}\) Moreover, under the name of amphoterin – it has been known to induce neurite extension, via interaction with a membrane receptor for advanced glycation end-products (RAGE).\(^{(20-22)}\) Additionally, a cell surface expressed form of HMGB1 has been described in the developing brain and in growing neurites, where it induces cell proliferation and neurite outgrowth by interacting and signaling through the RAGE.\(^{(17,21)}\)

Interestingly, resting human platelets express HMGB1 cytoplasmically.\(^{(23)}\) When platelets are activated, HMGB1 is translocated from the cytoplasm to the cell surface. The function of this relocation is not fully understood, but it is known that on cell surfaces HMGB1 associates with plasminogen and tissue

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**Cytokine-inducing peptide**

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**Fig. 1 Schematic drawing of human HMGB1.**
plasminogen activator and enhances plasmin generation and proteolysis.\(^2\)

### 2.3 HMGB1 and gene expression

HMGB1 endowed with ‘architectural’ capabilities is moderately sequence-specific, and helps build enhanceosomes by interacting with partner proteins and binding stably to the minor groove of DNA. Its acetylation/deacetylation signals enhanceosome assembly or disassembly. HMGB1 is a much more dynamic protein: it has no sequence specificity and it helps transcription factors and other nuclear proteins bind to their cognate sites by bending the DNA molecule. However, HMGB1 is rarely retained within the complex. Similarly, HMGB1 interacts with nucleosomes and promotes their sliding, but remains bound only for fractions of a second. It is argued that HMGB1 fluidizes chromatin - an action that appears opposite to that of histone H1.\(^2\)

Because of its abundance (about 1,000,000 molecules) in the nucleus of most cells, it was assumed that HMGB1 plays a functional role in the nucleus, although it has also been reported to be located extranuclearly, especially in neuronal cells and monocytes.\(^1\) HMGB1 interacts with histones in a manner that affects the chromatin structure, with HMGB1 opening up the chromatin coils. Until recently, when it was reported to be involved in inflammation, research on HMGB1 research was focused on its architectural roles in the assembly of nucleoprotein complexes and its facilitation of numerous nuclear transactions, including transcription, replication, V(D)J recombination, DNA transposition and DNA repair. In modulating transcriptional activity, HMGB1 interacts with steroid hormone receptors, NF-kB, p53, RAG1 recombinase, homeobox-containing proteins and TBP. Mice with genetic deletion of *Hmgb1* die shortly after birth, possibly as a result of a defect in activation of glucocorticoid receptor responsive genes, further supporting the important role of HMGB1 in regulation of gene transcription.\(^2\)

### 2.4 Regulation of cisplatin chemotherapy by HMGB1

HMGB1 interacts with specific DNA structural motifs such as those encountered with cisplatin damage, four-way junctions, and supercoils. HMGB1 binds specifically to cisplatin-modified 1,2-intrastrand d(GpG) and d(ApG) cross-links, but not to the DNA adducts formed by the clinically inactive isomer, trans-platinum(II).\(^2\) Both HMG domains A and B in full-length HMGB1 are bound to the site of cisplatin damage. The acidic C-terminal tail mainly interacts with domain B and linker regions rather than domain A in HMGB1.\(^2\)

Various studies have linked HMGB1 to cisplatin activity. *In vitro* nucleotide excision repair assay of platinated DNA is inhibited by HMGB1 addition.\(^3\) The cellular HMGB1 level may modulate cisplatin sensitivity by shielding the DNA adducts of cancer cells.\(^4\)** Consistent with this notion, hormone-induced HMGB1 expression in MCF-7 breast cancer cells correlates with increased cisplatin sensitivity.\(^5\)** In contrast, increased HMGB1 levels were noted in cisplatin-resistant human epidermoid cancer KB cells\(^5\) and human hepatocellular carcinomas.\(^6\)** Similar results were found in a human lung adenocarcinoma cell line that over-expressed HMGB2 by transfection. The HMGB2 protein is more than 80% identical to HMGB1.\(^7\)** Furthermore, enhanced HMGB1 binding to cisplatin-modified DNA was detected in resistant HeLa cells, although the HMGB1 protein levels remained normal.\(^8\)** Furthermore, a recent study found no significant difference between wild type HMGB1 and genetic knockout mouse embryonic stem cells following cisplatin treatment.\(^9\)** *Saccharomyces cerevisiae* became sensitive to cisplatin with the loss of an abundant HMG box protein, NHP6A.\(^10\)** These results suggest that HMGB1 participation in the efficacy of cisplatin treatment may be cell type dependent. Alternatively, HMGB1 sensitizes cells to cisplatin probably via a mechanism other than shielding DNA repair. The role of HMGB1 in cell sensitivity to cisplatin remains controversial.

### 3. HMGB1 as an Inflammatory Mediator

The cytokine activity of HMGB1 has been well-documented in many cell types, including macrophages/monocytes and endothelium, neutrophil, epithelium, dendritic and smooth muscle cells. Resting, non-activated inflammatory cells such as monocytes or macrophages contain HMGB1 in the nuclear compartment. When these cells are activated by lipopolysaccharide or inflammatory cytokines, they translocate the nuclear HMGB1 into the cytoplasm; HMGB1 is subsequently exocytosed, although the mechanism is not clear. Extracellular
HMGB1 then reaches responsive cells, either by diffusion in the immediate vicinity or via the blood stream to more distant compartments. Extracellular HMGB1 binds to specific receptors (e.g., RAGE). Following binding of HMGB1, signal transduction through RAGE activates several responses. Responses to the extracellular HMGB1 mediated signal depend on the cell type and include activation of inflammatory cells, proliferation of stem cells, and migration of several cell types towards the source of HMGB1.

Most recently, it has become clear that HMGB1 is released by dead cells and diffuses to the membrane of nearby cells, where it activates the RAGE receptor (and possibly other receptors). In this way, it alerts those cells that a neighbour has died and that they should act to repair the damage. In particular, HMGB1 attracts stem cells to the damaged tissue and promotes their proliferation. Remarkably, inflammatory cells have learned to secrete HMGB1. Excessive secretion of HMGB1 is involved in sepsis, rheumatoid arthritis, and probably several additional pathological conditions. Thus, HMGB1 can be released either passively by necrotic cells or actively by inflammatory cells.

### 3.1 Pioneer findings

Endotoxin, a constituent of gram-negative bacteria, stimulates macrophages to release large quantities of tumor necrosis factor (TNF) and interleukin-1 (IL-1), which can precipitate tissue injury and lethal shock (endotoxemia). Antagonists of TNF and IL-1 have shown limited efficacy in clinical trials, possibly because these cytokines are early mediators in pathogenesis.

The pioneer findings on HMGB1 as an inflammatory mediator, using a mouse model, were documented by K.J. Tracey and colleagues in 1999. HMGB1 protein was found to be released by cultured macrophages more than 8 hours after stimulation with endotoxin, TNF, or IL-1. Mice showed increased serum levels of HMGB1 from 8 to 32 hours after endotoxin exposure. Delayed administration of antibodies to HMGB1 attenuated endotoxin lethality in mice and administration of HMGB1 itself was lethal. Septic patients who succumbed to infection had increased serum HMGB1 levels, suggesting that this protein warrants investigation as a therapeutic target. Soon after these findings were published, numerous studies in humans as well as animals also pointed to the notion that HMGB1 is a late, better controlled mediator than other cytokines of inflammation in therapy.

### 3.2 Nuclear escape of HMGB1

How HMGB1 translocates extranuclearly was a mystery for a long time. Recently, the pathway of HMGB1 secretion was unraveled by Bianchi and colleagues. This secretion requires hyperacetylation of HMGB1 (to move it out of the nucleus), and specific secretory lysosomes. Lipopolysaccharide (LPS) or cytokines bind receptors and activate HMGB1-responsive cells (e.g., macrophages/monocytes). Upon activation, HMGB1 is relocated from the nucleus to the cytoplasm and subsequently is secreted via a vesicle-mediated secretory pathway. Inducing nuclear HMGB1 acetylation by stimulation with LPS or forced hyperacetylation by acetylases in resting macrophages also relocates HMGB1 from nuclei to cytosol toward secretion. Figure 2 briefly depicts pathways of HMGB1 secretion.

In most types of healthy cells, HMGB1 is nuclear but undergoes rapid cycles of binding and detachment from chromatin. When a cell undergoes necrosis, its membranes lose their integrity; HMGB1 is no longer constrained in the nucleus and passively diffuses out of the cell. On the contrary, when the cell activates its apoptosis program, as a late event its chromatin collapses and HMGB1 becomes tightly attached to the nuclear remnants. Thus, apoptotic
cells do not signal their own death because they retain HMGB1.

It was proved that wild-type necrotic cells evoke a strong inflammatory response from macrophages, whereas Hmgb1-/- necrotic cells cannot leak HMGB1 and have only a very mild inflammatory response. HMGB1 also causes inflammatory responses in various systems in vivo, such as brain, lung, gastrointestinal tract, joint, and heart. Excessive secretion of HMGB1 leads to systematic inflammation, sepsis and ultimately even death, both in mice and humans. HMGB1 is toxic to bacteria as well.

### 3.3 The inflammatory cascade triggered by HMGB1

HMGB1 activates inflammatory responses through multiple pathways including macrophage activation and release of proinflammatory cytokines; endothelial cell activation and increased expression of adhesion molecules; increased expression of PAI-1 and tPA, which are involved in regulation of coagulation; and increased epithelial permeability and bacterial translation in the gut. These pathways lead to a cascade of inflammatory responses that can cause tissue damage and even death. The inflammatory cascade triggered by HMGB1 is outlined in Figure 3.

What are HMGB1 signal transduction pathways? HMGB1 binds RAGE, TLR2, and possibly TLR4 and other receptors. Activation of RAGE has two main outcomes, activation of CDC42 and Rac, which regulate neurite outgrowth during neuron development and activation of Ras, MAPK pathways, and subsequently, NF-κB nuclear translocation. Activation of TLR2 (and/or TLR4) by HMGB1 causes recruitment of MyD88 and IL-1 receptor-associated kinase (IRAK), which subsequently activates the MAPK pathway and then NF-κB translocation, which triggers inflammatory responses. The signal pathways of cells in response to HMGB1 are summarized in Figure 4.

### 4. Anti-HMGB1 Treatment in Inflammatory Diseases

With respect to acute inflammation, HMGB1 has been documented to be of pathogenic relevance in sepsis, pneumonia and endotoxemia. Furthermore, HMGB1 mRNA levels were reported to be increased in experimental models of thermal injury and hepatitis. HMGB1 has also been reported as having a possible pathogenic role in chronic inflammatory conditions. Examples of this include the presence of extracellular/cytoplasmic HMGB1 in experimental arthritis models as well as in patients with rheumatoid arthritis and chronic myositis.

Sepsis, a potentially fatal clinical syndrome, is mediated by an early (e.g., tumor necrosis factor and IL-1) and late (e.g., HMGB1) proinflammatory
cytokine response to infection. Despite significant advances in intensive care therapy and antibiotics, severe sepsis accounts for 9% of all deaths in the United States annually. Specifically targeting early mediators has not been effective clinically, in part because peak mediator activity often has passed before therapy can be initiated. Late-acting downstream effectors that mediate sepsis lethality, such as HMGB1, may be more relevant therapeutic targets. In fact, any designs that interfere with HMGB1 release, block interaction between HMGB1 and its receptor, and/or disconnect HMGB1-induced intracellular signals of target cells are potentially therapeutic. Successful examples have been reported. Five promising examples of HMGB1 inhibition are presented below.

4.1 HMGB1 neutralizing antibody

A recent finding in the mouse HMGB1/TLR4 pathway in liver injury(44) is interesting. In contrast to the delayed role of HMGB1 in systemic inflammation in sepsis, HMGB1 acts as an early mediator of inflammation and organ damage in hepatic ischemia reperfusion (I/R) injury. HMGB1 levels were increased during liver I/R as early as 1 h after reperfusion and then time-dependently increased up to 24 h. Inhibition of HMGB1 activity with neutralizing antibody significantly decreased liver damage by I/R, whereas administration of recombinant HMGB1 worsened I/R injury. The kinase signaling underlying the inhibitory effect by neutralizing antibody was also tackled. Treatment with neutralizing antibody was associated with less phosphorylation of c-Jun NH(2)-terminal kinase and higher NF-κB DNA binding in the liver after I/R. Additionally, TLR4-defective (C3H/Hej) mice exhibited less damage in the hepatic I/R model than did wild-type (C3H/HeOuj) mice. Anti-HMGB1 antibody failed to provide protection in C3H/Hej mice, but successfully reduced damage in C3H/Ouj mice. Together, these results demonstrate that HMGB1 is an early mediator of injury and inflammation in liver I/R and implicate TLR4 as one of the receptors involved in the process.

4.2 Ethyl pyruvate

Ethyl pyruvate (EP) was recently reported to prevent inflammatory release of HMGB1 and lethality in mice with established lethal sepsis and systemic inflammation.(45) EP, a stable lipophilic pyruvate derivative, is an experimental therapeutic that effectively protects animals from ischemia/reperfusion-induced tissue injury. EP administration significantly improved survival in standard models of lethal hemorrhagic shock. It is reasonable to speculate that EP also might be protective in sepsis, because the pathogenesis of ischemia-reperfusion and hemorrhagic shock, like sepsis, depends on activation of early and late cytokine responses. Treatment with EP initiated 24 h after cecal puncture resulted in a survival rate of 88%, compared with 30% in mice given vehicle. EP treatment also significantly reduced circulating levels of HMGB1 in animals with established endotoxemia or sepsis. EP specifically inhibited activation of p38 MAP kinase and NF-κB, two signaling pathways that are critical for cytokine release, in macrophage cultures. Thus, EP treatment at clinically achievable concentrations may be a new strategy to pharmacologically inhibit HMGB1 release. Indeed, EP is a relatively nontoxic food additive and the protective effects occur with therapeutically achievable, safe doses.

4.3 Cholinergic agonists: nicotine

Cholinergic agonists were applied to inhibit HMGB1 release and improve survival in experimental sepsis.(46) The neurotransmitter acetylcholine inhibited HMGB1 release from human macrophages by signaling through a nicotinic acetylcholine receptor. Nicotine, a selective cholinergic agonist, was more efficient than acetylcholine and inhibited HMGB1 release induced by either endotoxin or TNF-alpha. Nicotinic stimulation prevented activation of the NF-κB pathway and inhibited HMGB1 secretion through a specific ‘nicotinic anti-inflammatory pathway’ that required the alpha7 nicotinic acetylcholine receptor (alpha7nAChR). In vivo, treatment with nicotine attenuated serum HMGB1 levels and improved survival in experimental models of sepsis, even when treatment was started after the onset of disease. These results reveal acetylcholine as a physiological inhibitor of HMGB1 release from human macrophages. They also suggest that selective nicotinic agonists for the alpha7nAChR might have therapeutic potential in the treatment of sepsis.

4.4 Antagonists of endogenous HMGB1

Antagonists of endogenous HMGB1 can also
reverse murine sepsis.\(^{[47]}\) Recently, it was found that serum HMGB1 levels increased significantly in a standardized model of murine sepsis beginning 18 h after surgical induction of peritonitis. Specific inhibition of HMGB1 activity beginning as late as 24 h after surgical induction of peritonitis significantly increased survival. The protective role of the antagonists against lethality was promising: Nonimmune IgG-treated controls had a 28% survival rate compared with a rate of 72% in the anti-HMGB1 antibody group. Only 28% of the mice given GST control survived compared with 68% of those given a box. Additionally, animals treated with either HMGB1 antagonist were protected against the development of organ injury, as evidenced by improved levels of serum creatinine and blood urea nitrogen. These observations demonstrate that specific inhibition of endogenous HMGB1 therapeutically reverses lethality of established sepsis, strongly suggesting that HMGB1 inhibitors can be administered in a clinically relevant time frame.

4.5 Thrombomodulin

Thrombomodulin (TM) is an endothelial anticoagulant cofactor that promotes thrombin-mediated formation of activated protein C (APC). Most recently, the N-terminal lectin-like domain (D1) of TM was demonstrated to display unique anti-inflammatory properties.\(^{[48]}\) TM, via D1, bound HMGB1, thereby preventing in vitro leukocyte activation, in vivo UV irradiation-induced cutaneous inflammation, and in vivo lipopolysaccharide-induced lethality. These data also suggest the therapeutic potential of a peptide spanning D1 of TM. These findings highlight a novel mechanism, i.e., sequestration of mediators through which an endothelial cofactor, TM, suppresses inflammation quite distinctly from its anticoagulant cofactor activity, thereby preventing the interaction of these mediators with cell surface receptors on effector cells in the vasculature.

5. Concluding Remarks

Inside the cell, HMGB1 acts as an architectural chromatin-binding factor that bends DNA and promotes protein assembly on specific DNA targets. Outside the cell, it binds with high affinity to RAGE (and/or other receptors) and is a potent mediator of inflammation. In this review, HMGB1 is proposed to be a cytokine, based only on its functions. The list of cytokines will probably expand (Table 1). These cytokines are multifunctional proteins that exert various well-defined primary roles and under special circumstances can exhibit cytokine functions as secondary roles. They target not only leukocytes but also other normal and neoplastic cell types. It is puzzling that these unrelated proteins that have very different primary roles can exert similar cytokine functions, basically recruitment and activation of leukocytes. It appears that these basic roles are achieved through various receptor types and signal transduction mechanisms as shown by different sensitivities to Bordetella pertussis toxin. However, the generated signals converge inside the cell and result in the activation of the MAP kinase pathway and subsequent activation of NF\(\kappa\)B, a key transcription factor of numerous genes required for an inflammatory response. Since they are ubiquitously expressed, they can serve to obtain optimally adapted cellular responses as convenient signals to immune cells and surrounding tissue that a particular event has occurred, for instance, tissue injury or necrosis in the case of HMGB1. Accumulating data on HMGB1 inhibition have proved it as an effective therapeutic target for inflammatory diseases including sepsis. Glycyrrhizin, present in large quantities in the roots and rhizomes of licorice (Glycyrrhiza glabra L.), also binds directly to HMGB1 and induces conformational changes in HMGB1.\(^{[50]}\) Its potential use in lowering HMGB1-mediated inflammation and sepsis

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Table 1. Primary and Signal Functions of Cytokines (Modified from Degryse & de Virgilio, 2003 \(^{[49]}\))
requires further study. The search for inhibitors or antagonists of HMGB1 has become an important issue.

Acknowledgements

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核蛋白 HMGB1 的细胞激素活性

孙念康1,2 趙清貴1

HMGB1 是一种流动性的染色质蛋白，当细胞受到损伤破裂时，HMGB1 会不耗能量地被释出，扮演一个讯号传递的角色，进而影响周围细胞。尚未活化的发炎细胞 HMGB1 存在细胞核；一旦被酶多糖或细胞激素活化，HMGB1 会耗能量地转移细胞质再被释出。目前已知细胞膜上至少有一个蛋白受体可以与细胞外的 HMGB1 作用，在不同的细胞可引起不同的反应，如细胞的分裂、移动、活化发炎或启动免疫反应。在本篇综论中，我们将介绍 HMGB1 如何扮演一个细胞激素的角色，包括它的分泌机制，讯号传递的路径，以及在发炎有关的疾病中所扮演的功能。最后，我们将会讨论在小鼠身上引发致命性的败血症、关节炎和肝臟损伤时，利用注射 HMGB1 的抗體以中和 HMGB1 的活性，可进一步缓解小鼠的病症。这些研究结果中发现，将 HMGB1 视为一种新的细胞激素，不但可进一步了解发炎相关的疾病，并可能在临床治疗上建立一个新的思考方向，而其重要性更明确地超越了已知细胞激素所扮演的角色。(長庚醫誌 2005;28:673-82)

關鍵字：关节炎，细胞激素，HMGB1，发炎，败血症。

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