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Review Article

High-Mobility-Group Box Chromosomal Protein 1 as a New Target for Modulating Stress Response

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Abstract
Major surgical procedures induce a systemic inflammatory response syndrome (SIRS) characterized by the overproduction of proinflammatory cytokines, which induces excessive stress and may trigger postoperative complications. This has prompted the hypothesis that drugs which relieve SIRS might improve the postoperative course of major surgery. One of the most promising targets for these drugs is high-mobility-group box chromosomal protein 1 (HMGB1). In 1999, HMGB1 was found to be a key late mediator of sepsis. It is now known to be associated with various kinds of acute and chronic inflammation, and is recognized as one of the most important danger signals in stress response. In this article, we present the latest information about HMGB1 and discuss its promise as a novel target for modulating stress response.

Key words Stress response · High-mobility-group box chromosomal protein 1 · Systemic inflammatory response syndrome · Multiple organ dysfunction syndrome · Alarmin · Pathogen-associated molecular pattern

Introduction

Surgery is often essential to remove disease-causing lesions; however, it can provoke excessive systemic inflammatory responses, leading to a disruption of homeostasis. In 1991, the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee proposed a set of definitions for systemic inflammatory response syndrome (SIRS).[1,2] Systemic inflammatory response syndrome is defined as at least two of the following abnormalities: fever or hypothermia; tachycardia; tachypnea; and leukocytosis or leukopenia.[1,2] Although SIRS includes diverse clinical conditions such as infection, trauma, burns, and acute pancreatitis, the physiological background is consistently characterized by the overproduction of chemical mediators such as cytokines, which can cause varying degrees of organ dysfunction.[3–9] Because the kinetics and magnitude of cytokine release influence the development of organ dysfunction, it is possible that modulating cytokine response could prevent SIRS from developing into more critical conditions.[10–15] However, the acute kinetics of most cytokines provides an extremely narrow therapeutic window for the effective use of specific cytokine inhibitors.[3,16] High-mobility-group box chromosomal protein 1 (HMGB1) was recently identified as a late mediator of systemic inflammation.[17] The downstream or late action of HMGB1 provides a wider time frame for clinical intervention against progressive inflammatory disorders.[16,18] This article analyzes the pathophysiological roles of HMGB1 and discusses the potential of HMGB1 as a clinically useful therapeutic target.

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HMGB1 as a Danger Signal

Molecular Characteristics

HMGB1, also referred to as amphoterin, was originally identified as a nuclear DNA-binding protein.[18] In 1973 it was also identified as a 30-kDa protein, which was first copurified from nuclei with histones, and termed "high mobility group 1" (HMG-1) protein because of its rapid mobility on electrophoresis gels.[19,20] HMGB1 localizes to the nucleus and cytoplasm of most cells, to the cell membrane of neuronal (neuroblastoma) cells, and to the filopodia of the advancing plasma membrane of neurites, where it colocalizes and interacts with tissue

plasminogen activator.[21,22] Membrane HMGB1 was termed "amphoterin" because it has marked dipolar charge properties.[21]

HMGB1 is produced by almost all cell types, and can migrate between the cytoplasm and nucleus in a cell-cycle-dependent manner.[23] The amino acid sequence of HMGB1 is highly preserved in different species, and contains a continuous stretch of negatively charged residues in the C-terminus and two internal repeats of positively charged domains known as the HMG A box and the HMG B box in the N-terminus.[24] The HMG boxes provide a secondary structure specific for DNA binding and contribute to the potential role of HMGB1 in DNA recombination, repair, replication, and gene transcription.[25–30] HMGB1 bends DNA and facilitates the binding of various transcription factors to their cognate sequences, including the steroid/nuclear hormones.[31] The nuclear localization of HMGB1 and its affinity for DNA are regulated through phosphorylation and acetylation, and it has been found to have a dynamic relationship with chromatin.[32–34] HMGB1-deficient mice are viable only for a few hours after birth.[35] The lack of chromosomal HMGB1 protein does not disrupt cell growth, but may affect the transcriptional regulation of certain genes such as those activated by the glucocorticoid receptor.[35]

Danger Signaling

In 1994, Matzinger proposed the concept of danger signaling to account for the inflammation that occurs in settings such as trauma and autoimmunity, which are void of infectious stimuli.[36] In this model, the inflammatory response is initiated in response to molecular patterns, which are associated with pathogens and some normal cellular components released by damaged cells during both infectious and sterile processes.[37] Molecular elements from pathogens that elicit an immune response, such as lipopolysaccharide (LPS), bacterial DNA, and viral RNA, are specific, generally invariant patterns termed pathogen-associated molecular patterns (PAMPs).[38–40] The cellular receptors that recognize these patterns are evolutionarily conserved and are called pattern recognition receptors.[40] This theory provides a plausible explanation as to why inflammatory responses following sterile injury closely mimic those seen during infection, with similar cytokine and chemokine production patterns.[41,42]

Release of HMGB1

HMGB1 is released passively during cellular necrosis by almost all cells that have a nucleus, and it signals to neighboring cells of ongoing damage.[43] However, HMGB1 is also secreted actively by immune cells such as monocytes, macrophages, and dendritic cells[17,44,45] (Fig. 1). The stimuli for secretion of HMGB1 from immune cells are diverse. In addition to PAMPs, endogenous molecules, such as cytokines released during other states of injury, can result in the secretion of HMGB1. Although first demonstrated with interferon-γ, macrophages also release HMGB1 in response to stimulation with tumor necrosis factor (TNF)-α, interleukin (IL)-1, and oxidative stress.[46–50] Interestingly, the PAMP and cytokine stimuli for HMGB1 secretion from macrophages occur through distinct pathways.[46]

Receptors of HMGB1

Several important receptors have been implicated in HMGB1 signaling, including the receptor for advanced glycation end products (RAGE) and members of the Toll-like family of receptors (TLRs; Fig. 1).[51–53] HMGB1 signaling through RAGE promotes chemotaxis and the

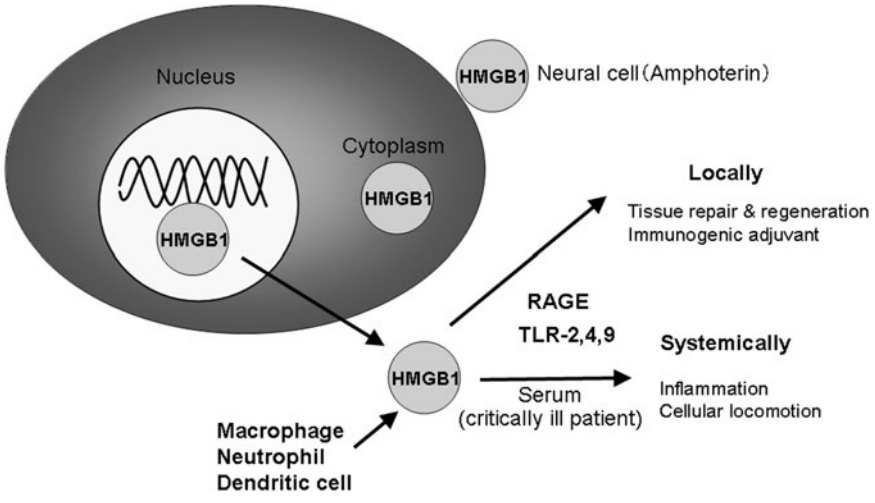

Fig. 1. High-mobility-group box chromosomal protein 1 (*HMGB1*) localizes to the nucleus and cytoplasm of most cells and to the cell membrane of neuronal cells. HMGB1 is released passively during cellular necrosis by almost all cells. HMGB1 is also secreted actively by immune cells such as monocytes, macrophages, and dendritic cells in response to stimulation with pathogen-associated molecular patterns and cytokines. HMGB1 shows not only proinflammatory functions but also restorative effects, leading to tissue repair and regeneration through receptor for advanced glycation end products (*RAGE*) and Toll-like receptors (*TLR*)

production of cytokines in a process that involves the activation of the transcription factor nuclear factor-κB (NF-κB).[54,55] Other RAGE-dependent effects of HMGB1 appear to involve the maturation and migration of immune cells, as well as the upregulation of cell surface receptors.[48,56–65] TLR2, TLR4, and TLR9 have all been shown to be HMGB1 receptors. The HMGB1 binding of TLR2 and TLR4 results in NF-κB activation; thus, it is likely that HMGB1 stimulation of these receptors can lead to cytokine release.[52,53]

Pathophysiologic Effects of HMGB1: Proinflammatory Effects

HMGB1 as a Cytokine

Cytokines have been defined as proteins that can be released from activated immunocytes and mediate diverse metabolic and immunological responses in other cells.[66] HMGB1 is actively released from activated immunocytes, such as macrophages, monocytes, and dendritic cells. Once released, HMGB1 can bind to cell-surface receptors such as RAGE, TLR2, and TLR4, and mediate various cellular responses, including chemotaxis and release of proinflammatory cytokines, such as TNF and IL-1.[52,67–69] Taken together, these observations characterize HMGB1 as a nonclassical, proinflammatory cytokine.

Pathophysiologic Effects of HMGB1

The proinflammatory activity of HMGB1 causes inflammatory responses in various organs. HMGB1 was initially implicated as an important endogenous signaling molecule in 1999 by Wang et al.,[17] who observed that serum concentrations of HMGB1 increased significantly 16–32 h after LPS administration in mice, and that the systemic administration of HMGB1 was lethal to wild-type mice.[17] Although early studies demonstrated HMGB1 as a late mediator of sepsis, recent findings indicate that HMGB1 plays an important role in models of noninfectious inflammation, such as autoimmunity, cancer, trauma, and ischemia/reperfusion injury (IRI). HMGB1 has also been studied in a number of organ systems in various pathological settings (Table 1).

Systemic Inflammatory Response

HMGB1 is associated with various infectious and noninfectious conditions related to SIRS, such as sepsis, hemorrhagic shock, trauma, IRI, disseminated intravascular coagulation (DIC), and major surgery. In relation to infectious conditions, HMGB1 is released systemically in murine models of endotoxemia and sepsis induced by cecal perforation[16,70]. Moreover, in one study, serum HMGB1 levels were significantly higher in 25 sepsis patients than in healthy volunteers, and were higher in patients who succumbed to disease than in survivors.[17] In relation to noninfectious conditions, elevated circulating levels of HMGB1 were described in a case report of hemorrhagic shock without evidence of infection.[71] In this patient, the serum HMGB1 levels increased significantly within 24 h after the onset of hemorrhagic shock and returned toward the baseline level as the clinical condition improved.[71] HMGB1 neutralizing antibodies ameliorate hemorrhage-induced acute lung injury as well as gut barrier dysfunction, ultimately improving the chance of survival.[72,73] HMGB1 also plays a central role in the initiation and propagation of inflammatory response following traumatic injury.[74] Moreover, there is much confirmatory evidence

Table 1. Pathophysiologic effects of high-mobility-group box chromosomal protein 1 (HMGB1)

- Systemic inflammatory response
  Sepsis, hemorrhagic shock, trauma, IRI, DIC, major surgery
- Respiratory system
  ALI, VILI, occult lung injury
- Cardiovascular system
  Myocardial infarction, atherosclerosis
- Musculoskeletal system
  Arthritis
- Central nervous system
  Sickness behavior (fever, anorexia, taste aversion, weight loss)
  Brain infarction
- Gastrointestinal tract
  Intestinal barrier function, inflammatory bowel disease
- Pancreas
  Pancreatitis

IRI, ischemia/reperfusion injury; DIC, disseminated intravascular coagulation; ALI, acute lung injury; VILI, ventilator-induced lung injury

that HMGB1 is involved in the initiation of inflammatory response following ischemia/reperfusion in the liver, heart, kidney, and brain. TLR4 signaling plays a dominant role in mediating the organ damage in IRI.[75–79] In addition, plasma HMGB1 levels are increased in patients with DIC, and HMGB1 in the systemic circulation induces DIC in rats.[80,81] Our previous clinical study on thoracic esophagectomy patients revealed a correlation between higher levels of HMGB1 in the immediate postoperative period as well as elevated preoperative serum HMGB1 concentrations and a complicated clinical course, indicating that elevated HMGB1 may play a role in the development of postoperative organ system dysfunction.[82]

Respiratory System

HMGB1 is associated with acute lung injury (ALI), ventilator-induced lung injury (VILI), and occult lung injury. Elevated HMGB1 levels are found in the plasma and lung epithelial lining fluid of patients with ALI and in mice instilled with LPS.[83] The intratracheal instillation of HMGB1 in mice causes ALI as manifested by neutrophil accumulation, lung edema, and increased pulmonary cytokine levels, including TNF, IL-1β, and MIP-2.[45] Lastly, treatment with anti-HMGB1 antibodies in mice exposed to intratracheal LPS significantly decreases lung edema and neutrophil accumulation but does not suppress LPS-induced pulmonary cytokines, indicating an important downstream role of HMGB1 in ALI.[45,83,84] Recently, HMGB1 was also suggested to be one of the deteriorating factors in the development of VILI and to be involved in the pathogenesis of occult lung injury in the residual lung after pneumonectomy.[85,86]

Cardiovascular System

HMGB1 is associated with myocardial infarction and atherosclerosis. In patients with myocardial infarction, a higher peak serum HMGB1 level is associated with pump failure, cardiac rupture, and in-hospital cardiac death.[87] HMGB1 is present in much larger quantities in atherosclerotic plaques than in normal arterial walls, and is associated with neointimal hyperplasia and in-stent restenosis.[88]

Musculoskeletal System

Biopsy samples from rheumatoid arthritis patients show elevated HMGB1 levels in synovial fluid.[89,90] Accordingly, high levels of HMGB1 have been observed in rats with adjuvant arthritis.[90] Immunostaining of synovial tissues from adjuvant-induced arthritis rats show that HMGB1 is abundantly expressed as a nuclear, cytoplasmic, and extracellular component when compared with specimens from normal rats, in which HMGB1 is primarily confined to the nucleus.[90] The intra-articular administration of HMGB1 induces the onset of arthritis in mice, suggesting an important role of HMGB1 in the pathogenesis of arthritis.[91–93]

Central Nervous System

The intracerebrocentricular administration of HMGB1 in mice increases their brain TNF, IL-1, and IL-6 expression, and induces symptoms such as fever, anorexia, taste aversion, and weight loss.[94,95] HMGB1 also plays a critical role in brain infarction through the amplification of plural inflammatory responses in the ischemic region. This effect could be attenuated by the intravenous injection of neutralizing anti-HMGB1 antibody in rats.[96]

Gastrointestinal Tract

HMGB1 and B-box impair intestinal barrier function in mice, and increase ileal mucosa permeability and bacterial translocation to the mesenteric lymph nodes. This impairment is via a mechanism that depends on nitric oxide formation.[97] In mice with chemically induced colitis, serum HMGB1 levels increase and the inhibition of HMGB1 by the anti-HMGB1 antibody reduces inflammation in the colon.[98] These facts suggest that HMGB1 is potentially a useful target for the treatment of inflammatory bowel disease.

Pancreas

Serum HMGB1 levels increase significantly in patients with severe acute pancreatitis and correlate with disease severity.[99] This indicates that HMGB1 may act as a key mediator for inflammation and organ failure in severe acute pancreatitis.

Beneficial Roles of HMGB1: Role of HMGB1 in Tissue Repair and Preconditioning

Dual Role of HMGB1

In contrast to the proinflammatory functions of HMGB1, there is much evidence that this molecule also has restorative effects, promoting tissue repair and regeneration (Table 2).[100] HMGB1 induces a concentration-dependent activity that varies from beneficial to pathological.[18] Similar to other proinflammatory cytokines, excessive levels of HMGB1 result in an uncontrolled inflammatory response that can be more dangerous than the original insult, inducing tissue injury and organ failure.[43,44,93] However, moderate amounts of

Table 2. Beneficial effects of HMGB1

• Tissue repair and regeneration
Chemoattractant
Promotion of migration and proliferation of regenerative cells
Healing process after cardiac infarction
Promotion of wound healing in diabetic skin
• Preconditioning

HMGB1 induce a beneficial immune response to confine infection or tissue damage and promote wound healing and tissue regeneration.[18] Structural characteristics partially account for this dual nature of HMGB1. Several studies have identified the B-box domain as important for many of the proinflammatory properties of HMGB1, including cytokine release.[56,101] Conversely, the A-box does not possess proinflammatory properties and instead competes with HMGB1 for binding sites, leading to attenuation of the inflammatory cascade.[16]

HMGB1 in Tissue Regeneration and Repair

In 2001, HMGB1 was first shown to function as a chemoattractant, when cytoskeleton reorganization and cell migration were induced in rat vascular smooth muscle cells.[102] In 2004, another study highlighted the use of HMGB1 in promoting migration and proliferation of regenerative cells to the sites of inflammation and injury.[103] Cell proliferation with HMGB1 stimulation was noted to increase in a dose-dependent manner, and in vitro and in vivo experiments showed that the migration of mesoangioblasts functioned in a dose-dependent manner through interactions with the RAGE receptor. More recent evidence suggests that the HMGB1 activation of homing of endothelial progenitor cell to ischemic tissues, to increase neovascularization, involves an integrin-dependent mechanism.[104]

In a model of myocardial infarction, exogenous HMGB1 was shown to be beneficial in promoting left ventricular function and myocyte regeneration.[105] Moreover, HMGB1 blockade with systemic administration of anti-HMGB1 antibody in a rat myocardial infarction model aggravated left ventricular remodeling, suggesting that endogenous HMGB1 may play an essential role in the healing process after cardiac infarction.[87]

HMGB1 levels are reduced in the skin of diabetic humans and mice. Moreover, topical application of HMGB1 to murine diabetic skin wounds promotes wound closure, and the effect could be impaired if HMGB1 A-box is used to inhibit endogenous HMGB1.[106]

HMGB1 and Preconditioning

Preconditioning is a phenomenon whereby the delivery of a minor insult prepares the body to better withstand a more severe insult.[107] HMGB1 has a preconditioning ability. For instance, HMGB1 administration 1 h prior to the onset of injury results in dose-dependent protection, as evidenced by decreased circulating biochemical markers of liver damage and decreased serum TNF-α and IL-6 levels.[108] This effect seems to be mediated through the inhibition of the TLR4 signaling pathway.[108] Using HMGB1 as a preconditioning stimulus could be a beneficial application of HMGB1 in the injury state.

HMGB1 and Cancer

There are many reports that HMGB1 plays a role in cancer development and metastasis, with RAGE-HMGB1 signaling promoting the spread of most tumor types, including breast, colon, melanoma, prostate, pancreatic, and lung cancer.[109] This suggests that all options inhibiting HMGB1 could work as anticancer treatments.

HMGB1 as a Prognostic Marker

We reported that the preoperative serum concentrations of HMGB1 in patients who underwent thoracic esophagectomy were significantly correlated with the postoperative duration of SIRS, of mechanical ventilation, and of intensive care unit stay.[82] Hatada et al. reported that plasma HMGB1 levels in patients with suspected DIC correlated with the DIC score and sepsis-related organ failure assessment score.[80] These facts suggest the potential of HMGB1 as a prognostic marker of critically ill patients.

HMGB1 as a Therapeutic Target

Theoretic Strategies for HMGB1 Modulation

As mentioned earlier, HMGB1 induces a concentration-dependent activity that varies from beneficial to pathological. Therefore, the basic strategy for modulating HMGB1 dynamics should be to reduce HMGB1 when HMGB1 is excessive for the patient and to restore HMGB1 when HMGB1 is insufficient for the patient.

Table 3. Potential HMGB1 eradication therapies

- Biological agents
  Anti-HMGB1 antibody
  HMGB1 A box peptide
  Soluble RAGE, anti-RAGE antibody
  Thrombomodulin
- Small-molecule chemical compounds
  Ethyl pyruvate
  Cholinergic agonists (nicotine, acetylcholine)
  Stearoyl lysophosphatidylcholine
  Steroidlike pigment tanshinone IIA
  Glycyrrhizin
  Sivelestat, nafamostat, antithrombin III, γ-globulin
- Others
  Hemoperfusion

RAGE, receptor for advanced glycation end products

In the critical setting, severe local inflammation promotes overproduction of HMGB1 and induces its spillage into the systemic circulation, resulting in the "metastasis" of inflammation to other organs. However, thrombomodulin prevents not only local coagulation but also local inflammation, from being systemic by binding to HMGB1;[110,111] therefore, inhibiting HMGB1 in the systemic circulation could be a promising therapy for critically ill patients (Table 3).

Inhibitors of HMGB1: Biological Agents

HMGB1-specific antibodies have been shown to protect mice against endotoxin and sepsis lethality.[16,17] Similar protective effects were observed with HMGB1 A-box peptide, a competitive antagonist of HMGB1 cytokine activity.[16] Antibodies against HMGB1 or recombinant A-box peptide have also been found to ameliorate the symptoms of collagen-induced arthritis.[92] Humanized anti-HMGB1 monoclonal antibodies could therefore find applications in both acute and chronic inflammatory diseases. Blockage of the RAGE signaling pathways could also result in attenuation of the proinflammatory effects of HMGB1. Several strategies, such as the administration of soluble forms of RAGE or the blocking of the Fab fragment derived from anti-RAGE and/or anti-HMGB1 IgG, have been reported.[112,113]

Thrombomodulin has recently been shown to bind to HMGB1 so that thrombin–thrombomodulin complexes can effectively degrade HMGB1 into a less proinflammatory form.[110,111,114] This means that recombinant thrombomodulin can promote the degradation of HMGB1 and suppress the proinflammatory effects of HMGB1.[114] Thrombomodulin can also suppress coagulatory responses; therefore, recombinant thrombomodulin should be a promising therapeutic option against DIC or sepsis.[114]

Inhibitors of HMGB1: Small-Molecule Chemical Compounds

Several small-molecule chemical compounds have been used to inhibit HMGB1 proinflammatory activities in vivo. These pharmacological agents belong to the class of cytokine-release inhibitory drugs (CRIDs) and include ethyl pyruvate, the cholinergic agonists nicotine and acetylcholine, stearoyl lysophosphatidylcholine, and steroid-like pigment tanshinone IIA.[115–118] These agents were found to interfere specifically with HMGB1 release from the nucleus into the extracellular space, without affecting HMGB1 mRNA or protein levels.[115,116] In contrast, many other steroidal drugs and nonsteroidal anti-inflammatory drugs failed to significantly inhibit HMGB1 extracellular release.[118] The HMGB1 CRIDs have shown impressive efficacy in animal models of lethal endotoxemia and sepsis, with protective effects at therapeutically achievable, safe doses, supporting the therapeutic potential of these inhibitors in HMGB1-mediated human inflammatory diseases.[115–118]

Another molecule, glycyrrhizin, inhibits the chemotactic and mitogenic activities of HMGB1.[119] Unlike CRIDs, glycyrrhizin does not interfere with the release of HMGB1, but directly inhibits its extracellular cytokine activities.[119] This means that glycyrrhizin can inhibit not only actively released HMGB1 but also passively released HMGB1. However, the affinity of glycyrrhizin for HMGB1 is relatively modest and will need to be improved for any therapeutic application.[119]

Several other commercially available drugs, such as sivelestat, nafamostat, antithrombin III, and γ-globulin, have also been suggested to modulate inflammatory response through HMGB1-related mechanisms.[120–124]

Others

It has been suggested that direct hemoperfusion using a polymyxin B-immobilized fiber column reduces HMGB1 levels in septic patients.[125]

Alarmin: A New Concept in Danger Signals

A new awareness of the close relationship between trauma- and pathogen-evoked responses emerged from the EMBO Workshop on Innate Danger Signals and HMGB1, which was held in February 2006 in Milan, Italy.[38,126] At the end of the meeting, the term "alarmin" was proposed to differentiate the endogenous molecules that signal tissue and cell damage (Table 4).[38] The exogenous PAMPs and endogenous alarmins are subgroups of the larger category of danger signals termed damage-associated molecular patterns (DAMPs) (Table 5).[38,126] The molecule that fits all of the criteria for alarm-

Table 4. Definition of alarmins

1	Passively released by necrotic cells, not by apoptotic cells
2	Actively secreted by immune cells
3	Recruit and activate receptor-expressing cells of the immune system
4	Promote the reconstruction of the damaged tissue

Table 5. Damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and alarmins

DAMPs	
PAMPs (exogenous)	Alarmins (endogenous)
Lipopolysaccharide	HMGB1
Bacterial DNA	S100 protein
Viral RNA	Hepatoma-derived growth factor
	Heat shock proteins
	Interleukin-1α
	Uric acid

ins exemplarily is HMGB1. Because alarmins are a diverse group of ubiquitous molecules implicated in nearly all inflammatory states, understanding and ultimately modulating their activity may allow us to control the inflammatory process.

Summary

A growing number of reports describe the specific functions of HMGB1 on cells of the immune system and its role in important disease states. Not only HMGB1, but other alarmins seem to be promising targets for various acute and chronic diseases including cancer, although few human-subject studies have been conducted. Interestingly, in addition to their proinflammatory roles, alarmins have several beneficial effects that promote tissue regeneration and repair. Understanding alarmins and their complex effects on the immune system may lead to the development of novel strategies to attenuate inflammation and promote tissue regeneration and repair in various clinical states. Further investigation of the effects of alarmins on humans is warranted.

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