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The alarmin functions of high-mobility group proteins

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Abstract

High-mobility group (HMG) proteins are non-histone nuclear proteins that bind nucleosomes and regulate chromosome architecture and gene transcription. Over the past decade, numerous studies have established that some HMG proteins can be released extracellularly and demonstrate distinct extracellular biological activities. Here, we will give a brief overview of HMG proteins and highlight their participation in innate/inflammatory and adaptive immune responses. They have the activities of alarmins, which are endogenous mediators that are rapidly released in response to danger signals initiated by infection and/or tissue damage and are capable of activating innate and adaptive immunity by promoting the recruitment and activation of antigen-presenting cells (APCs).

Keywords

High-mobility group protein; Alarmin; Dendritic cells; Immune response

1. HMG superfamily proteins

HMG proteins consist of a superfamily of nucleosome-binding proteins that were discovered more than 30 years ago [1]. HMG proteins are classified into HMGA, HMGB, and HMGN families [2,3]. HMGA family consists of four members (HMGA1a, 1b, 1c, and 2), each containing two to three “AT” hooks in the N-terminal portion of the molecule which enable HMGA to preferentially bind AT-rich regions of DNA. HMGB family has three members (HMGB1–3), each containing two “box” domains (A and B boxes) in the N-terminal portion of the molecule. The HMGN family contains five members (HMGN1, 2, 3, 4, and NBD-45) and is characterized by a cationic nucleosome-binding domain in the N-terminal portion of the molecule. Common to and characteristic of all HMG proteins is a C-terminal tail rich in acidic amino acid residues.

HMG proteins are ubiquitously present in almost all embryonic tissues. The expression of most members, such as HMGA1, 2, HMGB2, 3, and HMGN1, 2, is downregulated during ontogenic development [3–10]. In adults, HMGB1 is expressed at a high level in all cell types, whereas other HMG proteins are more selectively expressed in highly proliferative

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tissues that undergo constant turnover and differentiation, such as lymphoid tissues, testis, stem cells, and epithelial cells [3,4,8,10,11]. HMGN proteins appear late in evolution and are only found in vertebrates [3]. Inside the nucleus, HMG proteins exert diverse functions such as controlling chromatin architecture and dynamics, modifying the transcription of certain genes, and regulating DNA repair, cell differentiation, and ontogenic development, which will be the subjects of other reviews in this series.

Some HMG proteins, such as HMGB1 and members of HMGN family can be released from either injured necrotic cells or activated monocytes/macrophages, dendritic cells, and NK cells. HMGB1 release can be initiated by PAMPs, bacteria, ischemia/reperfusion-induced hypoxia, or proinflammatory cytokines [12–20]. While the extracellular release of HMGN family members has not been studied in detail, HMGB1 release by activated monocytes/macrophages involves a crucial initial acetylation on many of the 43 lysine residues of HMGB1 in the nucleus, followed by redistribution of HMGB1 from the nucleus to endolysosomes and finally exocytosis [14,17,21]. Release of HMGB1 by hepatocytes under hypoxic conditions relies on the generation of reactive oxygen species and calcium/calmodulin-dependent kinases [19]. LPS-induced HMGB1 release by monocytes and macrophages requires phosphorylation of HMGB1 by PKC and the presence of Ca^{2+} [22]. Recently, in a model of mouse lung inflammation caused by *Klebsiella pneumoniae*, the systemic release of systemic HMGB1 was found to be strictly dependent on NLRP3 and ASC, two critical components of the NLRP inflammasome inflammatory pathway [20].

HMG proteins in the extracellular milieu, in particular HMGB1, have also been shown during the last decade to have diverse activities in mediating cell migration, tumor invasiveness, neuronal innervation, inflammation, immunity, wound healing and repair [17,23–25]. We will focus on the alarmin functions of extracellular HMG proteins and their participation in inflammation and immunity.

2. Alarmin concept

During the 1990s, two popular models were developed to explain how the immune system is activated to mount innate and adaptive immune responses. The “infectious non-self” model proposed by Charles Janeway suggested that immune responses are initiated by professional antigen-presenting cells (APCs) that are activated based on the recognition of evolutionarily distinct pathogen-associated molecular patterns (PAMPs) (e.g. lipopolysaccharides or other microbial components) by a set of germ-line encoded pattern-recognition receptors (PRRs) [26]. This model ingeniously encompasses pathogen recognition, costimulation, and self–nonself discrimination, and elegantly explains how immune responses are induced by infections or enhanced by adjuvants containing certain microbial components. This hypothesis provided a theoretical framework that drove the subsequent identification of PRRs such as Toll-like receptors (TLRs) [27]. However, the Janeway’s model cannot easily explain the innate/inflammatory and immune responses that occur in autoimmune disorders, graft rejection, allergy, or sterile inflammation. The alternative danger model put forward by Polly Matzinger proposed that immune responses are induced by danger signals derived from stressed or injured cells and tissues, such as those exposed to pathogens, toxins, mechanical damage, and so forth, rather than recognition of components of non-self

infectious microorganisms[28]. This model provides rational explanations not only for pathogen-induced immunity but also for immune responses that occur in the absence of microbes. However, subsequently there was some redefinition as to what exactly would be considered “danger signals.” Initially, heat-shock proteins and any internal molecules that can activate APCs when released were proposed to be danger signals. Later addition to the list of danger signals included both endogenous and exogenous moieties based on their sources, such as interferon, IL-1, TNF, CD40 ligand, ATP, mammalian DNA, degraded products of extracellular matrices, haptens, toxins, uric acids, and even microbial components [29]. In 2004, PAMPs and danger signals derived from damaged tissue were proposed to be collectively termed damage-associated molecular patterns (DAMPs) based on their shared chemical property of hydrophobicity and function of stimulating the immune system [30].

In the late 1990s and early 2000s in the course of studying unexpected effects of mammalian antimicrobial peptides and proteins (AMPs) on various subsets of leukocytes, some AMPs such as defensins and cathelicidins were also found to have unique dual effects on host cells of inducing both the chemotactic migration and activation of APCs including dendritic cells (DCs) and macrophages [31–33]. The APC-attracting effect was mediated by G α -protein-coupled receptors (GiPCRs), whereas the APC-activating effect was mediated by other receptors, some of which were identified to be PRRs [31,32,34,35]. Administration of such AMPs together with an antigen *in vivo* caused the recruitment of DCs and enhanced adaptive immune responses [33–36]. Subsequently, it became clear that not all AMPs had these effects. On the other hand, some endogenous mediators that are not traditionally considered as AMPs, such as high-mobility group box-1 protein (HMGB1), were also shown to exhibit similar chemoattracting and activating effects on DCs, as well as the capacity to enhance adaptive immune response [12,13]. By 2004, it had been established that the recruitment and maturation of DCs, the professional APCs, are crucial for the induction of immune responses based on the activation of antigen-specific naïve T cells [37]. Thus, those structurally distinct endogenous mediators that rapidly become available in peripheral tissues in response to danger signals (e.g. infection and/or injury) and are capable of enhancing the induction of innate and adaptive immune responses by promoting the recruitment and maturation of APCs were proposed to be “alarmins” because they are generated in response to danger (e.g. infection and/or injury) and serve to alarm the immune system [38,39].

Alarmins are often constitutively stored in cells of the innate immune system (e.g. granulocytes, epithelial cells, and keratinocytes) as components of the granules, cytoplasm or nucleus. Most alarmins can also be induced to be synthesized in response to proinflammatory cytokines and PAMPs. Alarmins are rapidly released by degranulation and/or cell necrosis in response to danger (i.e. infection and/or injury) and also promote the restoration of damaged tissue, and therefore, can be considered to be an endogenous subset of DAMPs engaged in host defense [23]. Currently known alarmins include defensins, cathelicidins, eosinophil-derived neurotoxin, lactoferrin, some high-mobility group (HMG) proteins, granulysin, and probably also ATP and histamine, while endogenous mediators that may eventually prove to be alarmins include some members of the S100 family proteins,

heat-shock proteins, and certain degraded products of extracellular matrix (e.g. hyaluronan and heparan sulfate).

3. Extracellular HMGB1 acts as an activator for APCs

The discovery of the role(s) of HMGB1 in inflammation and immunity can be credited to Kevin Tracey's group, who first reported that HMGB1 was released by macrophages and acted as a late mediator of endotoxin-induced septic shock [13]. Since then, HMGB1 has been shown to have many diverse effects on various leukocytes (Table 1). HMGB1 has been shown to activate human peripheral blood monocytes and macrophages to produce multiple cytokines such as TNF α , IL-1, IL-6, IL-8 and MIP-1 α and MIP- β [40–43]. Treatment of human neutrophils with HMGB1 result in the activation of NF- κ B and production of a variety of proinflammatory cytokines, which depends on the activation of PI-3K and p38 MAPK [44]. HMGB1 activates cultured astrocytes, leading to the expression of many inflammatory mediators including cyclooxygenase-2 and many chemokines [45]. HMGB1 is also capable of activating DCs [12,46–48]. Incubation of myeloid immature DCs with HMGB1 induces their maturation as evidenced by upregulation of costimulatory (e.g. CD83, CD80, CD86) and MHC class I and class II molecules, enhanced production of cytokines including TNF α , IL-1, IL-6, IL-8, and IL-12, development of the capacity to migrate in response to lymphoid-homing chemokine CCL21, and acquisition of the capacity to stimulate the proliferation of allogeneic T lymphocytes [12,46–48]. The capacity of HMGB1 to activate macrophages and DCs is located in the B box domain [41,47,48]. Recently, HMGB1 secreted by NK cells or in the form of complexes with DNA-containing immune complex or CpG-ODN was shown to activate both B cells and plasmacytoid DCs, leading to the upregulation of production of inflammatory cytokines including TNF α , IL-6, and IL-12 [15,16,49,50]. Therefore, HMGB1 is an activator for various leukocytes, in particular, APCs including monocytes/macrophages and DCs.

The activation of mouse macrophages and plasmacytoid DCs by HMGB1 depends in part on the receptor for advanced glycation end-products (RAGE) [50,51]. RAGE is a member of the immunoglobulin superfamily of cell surface molecules [52,53]. The capacity of HMGB1 to mediate cardiac inflammation in response to ischemia-reperfusion injury is clearly dependent on RAGE [54]. Therefore, RAGE is a receptor required for HMGB1 to mediate its inflammatory and immunoenhancing effects. On the other hand, HMGB1-induced NF- κ B activation and cytokine production in phagocytes relies on both TLR2 and TLR4 [55,56]. Recently, HMGB1 was detected in DNA-containing immune complexes often present in the serum of patients with systemic autoimmune diseases (e.g. systemic lupus erythematosus) [49,57]. The activation of B cells and/or plasmacytoid DCs by HMGB1-and DNA-containing immune complexes or by complexes of HMGB1 and CpG-ODN is crucially dependent on both RAGE and TLR9 [15,49]. Therefore, the activation of leukocytes, including DCs, by HMGB1 preparations appears to be mediated by multiple receptors including RAGE and TLR2, 4, and/or 9. The down-stream signal pathways of HMGB1-induced activation of APCs include the activation of NF- κ B and multiple MAPKs [43,47,51,55,56], which emulate the signal pathways triggered by the activation of RAGE and TLRs [58,59].

The triggering of so many different receptors by HMGB1 preparations was surprising. However, it also has been reported that highly purified eukaryotic HMGB1 induces very little production of proinflammatory cytokines [60,61]. Consequently, HMGB1 by itself appears not to possess leukocyte-activating effects and the previously reported proinflammatory effects of HMGB1 were probably due to 'some contaminants' of bacterial origin, such as endotoxin or lipoproteins, since in most previous studies recombinant *E. coli*-derived HMGB1 was utilized. This notion gained momentum following reports showing that HMGB1 has a great capacity to bind to other proteins [62], PAMPs such as LPS [63], DNA [15,49,57], and IL-1 [64]. Nevertheless, several other lines of evidence suggest that contamination by PAMPs can not satisfactorily explain the *in vivo* proinflammatory and immunostimulatory effects of HMGB1. The inflammatory responses induced by mechanical trauma or ischemia/reperfusion injury are known to be predominantly mediated by HMGB1 [54,65–69]. In those *in vivo* sterile inflammation models in which no exogenous HMGB1 is administered, the participation of exogenous PAMPs is unlikely, yet HMGB1-mediated inflammatory responses fail to occur TLR4-deficient mice, and therefore are still dependent on the presence of TLR4 [65–68]. Another line of evidence demonstrating the critical role of TLR4 in HMGB1-mediated immune responses comes from studies of immunogenic tumor cell death induced by irradiation or anti-tumor chemotherapeutic drugs [70], in which HMGB1 released by dying tumor cells *in vivo* has been shown to stimulate anti-tumor immune responses by triggering TLR4-expressing DCs [70,71]. In the case of TLR2, HMGB1 released from 'late apoptotic' cells in the form of HMGB1-nucleosome complex has been shown to induce the activation of macrophages and DCs and to stimulate anti-dsDNA and anti-histone IgG responses in a TLR2-dependent manner [57]. In addition, TLR2 has also been shown to mediate HMGB1-induced inflammation in a model of renal injury [72] and HMGB1-mediated immunity against glioblastoma [73]. Thus, it is clear that *in vivo*, HMGB1 activates macrophages and DCs by engaging multiple receptors including RAGE, TLR2, TLR4, and TLR9. Whether HMGB1 engages all the receptors by itself or in the form of complexes with other endogenous TLR agonists remains to be determined.

4. HMGB1 participation in APC recruitment

HMGB1 has been shown to be chemotactic for many somatic cell types such as neuronal cells, smooth muscle cells, mesodermal stem cells (mesoangioblasts), bone marrow mesenchymal stem cells, keratinocytes, and fibroblasts [25,52,74–77]. HMGB1 generated by monocytes promotes their transendothelial migration, suggesting a potential role of HMGB1 in affecting the recruitment of APC [78]. Purified mammalian HMGB1 induces the chemotactic migration of immature DCs [46], may therefore act as a direct chemoattractant to promote the recruitment of APCs. A very recent study demonstrates that HMGB1 promotes SDF-1 α -induced migration of macrophages and DCs by stabilizing SDF-1 α [79]. Since the interaction of SDF-1 α and its receptor CXCR4 contributes to both the recruitment of immature DCs to sites of inflammation and homing of mature DCs to the secondary lymphoid organs [80], HMGB1 may also participate indirectly in promoting the recruitment and homing of DCs by stabilizing SDF-1 α .

One receptor that mediates the effect of HMGB1 on the recruitment of various target cells is RAGE [52,74,75,77]. HMGB1-induced migration of monocytes/macrophages and DCs can

be blocked with anti-RAGE neutralizing antibodies or by the HMGB1 antagonist Box A [46,78,79]. The importance of HMGB1-RAGE interaction in mediating DC recruitment and homing has recently highlighted by the lack of homing of RAGE^{-/-} DCs into regional lymph nodes of mice that were injected into the footpads [81]. *In vivo*, the presence of RAGE on the surface of neutrophils is essential for HMGB1-induced neutrophil recruitment [82]. Therefore, RAGE appears to be an essential receptor for HMGB1-mediated cell recruitment.

Other receptor(s) may also participate in HMGB1-induced cell recruitment. The migration of smooth muscle cells and DCs in response to HMGB1 can be inhibited by pertussis toxin [46,74]. Since pertussis toxin is a selective inhibitor of G α i protein-coupled receptors (GiPCRs) that mediate the migration of essentially all types of cells in response to all chemoattractants including chemokines [83,84], it is therefore possible that HMGB1 also triggers an yet unidentified GiPCR. In addition, HMGB1-induced *in vivo* recruitment of neutrophils is also abrogated in Mac-1 knockout mice, demonstrating that Mac-1 by promoting the adhesion of migrating cells may also play a role in HMGB1-mediated recruitment of leukocytes [82].

The down-stream signaling events of HMGB1-mediated cell recruitment are still incompletely identified. Several previous studies demonstrate that HMGB1-induced migration and recruitment of mesoangioblasts and fibroblasts require the activation of NF- κ B, Erks, and Src family kinases, however, it has not been determined whether similar intracellular signal transducers also participate in the HMGB1-induced migration and recruitment of APCs [77,85]. In general, signaling of GiPCR does not have potent activating effects on host cells, which led us to identify additional distinct receptors involved in the activation of APCs by alarmins.

5. Contribution of HMGB1 to the induction of innate/inflammatory and adaptive immune responses

Exposure of macrophages and DCs to HMGB1 in any tissue would induce an innate/inflammatory response by promoting the production of many proinflammatory mediators including proinflammatory cytokines such as TNF α , IL-1, and IL-6. Indeed, HMGB1 has been shown to participate in inflammatory responses such as endotoxin-induced sepsis [13,86,87], autoimmune inflammation (e.g. rheumatoid arthritis, systemic lupus erythematosus, etc.) [88–93], and trauma-induced inflammation [40,65–68,94,95]. In addition, the participation of HMGB1 in inflammation has also been demonstrated by studies showing that various innate/inflammatory responses can be ameliorated by strategies based on abrogating the effect of endogenous HMGB1. For example, the septic model of acute inflammation can be inhibited by reducing the release of HMGB1 [86,93,96–100]. In addition, HMGB1-mediated inflammatory responses can also be reduced by strategies aiming at blocking the activity of extracellular HMGB1 by HMGB1-neutralizing antibody, HMGB1 box A fragment, soluble RAGE or anti-RAGE neutralizing antibody, or by thrombomodulin [41,69,87,94,101–103]. Thus, it is well established that HMGB1 is a critical mediator of inflammation.

The induction of adaptive immune response begins in the peripheral tissue where immature DCs are recruited, take up antigens, and are activated by various mediators including alarmin(s) to become mature DCs that subsequently home to the secondary lymphoid organs to present antigenic epitopes in the context of MHC class I and II molecules to naïve T cells resulting in their activation. The participation of endogenous extracellular HMGB1 in the initiation of antigen-specific immune response was initially demonstrated by its capacity to enhance antibody response to soluble antigens and cellular immune response against poorly immunogenic lymphoma [12]. HMGB1 released by dying tumor cells is one critical mediator for the activation of DCs and subsequent development of anti-tumor immunity in immunocompetent mice [70,71], an observation in full agreement with the essential role of HMGB1 in the enhancement of adaptive immunity. Nucleosomes from “late apoptotic” cells that contain HMGB1 in the form of nucleosome-HMGB1 complexes can induce the generation of anti-DNA and anti-histone antibodies, whereas nucleosomes derived from living cells, or those from “late apoptotic” cells that are devoid of HMGB1, cannot do so, also demonstrating a critical role of HMGB1 in the augmentation of antigen-specific immune response [57]. Very recently, the importance of HMGB1 in the enhancement of immune response is also demonstrated in allograft rejection, a process known to be mediated by both inflammatory and immune responses. For example, HMGB1 is critically involved in the acute rejection reaction of allograft [104], which can be ameliorated by blockade of either HMGB1 [104] or its RAGE receptor [105].

There is fascinating data suggesting HMGB1 is also involved in wound repair. Wound repair is a complex process that consists of an immediate phase of clotting, and early phase of inflammation, a subsequent phase of “proliferation, migration, and contraction,” and a final phase of resolution [106]. The participation of HMGB1 in inflammatory response indicates that HMGB1 plays a role in the inflammatory phase of wound repair. In addition, HMGB1 is also involved in the “proliferation, migration, and contraction” phase of wound repair by promoting the migration, proliferation, and/or differentiation of stem cells [107], smooth muscle cells [74], mesoangioblasts [75,77], endothelial precursor cells [108], and keratinocytes [25,109]. The potentially pivotal role of HMGB1 in repair has also been supported by studies showing that administration of HMGB1 results in greatly improving the recovery of rat from heart damage by hypoxic ischemia-reperfusion [54,110,111].

The importance of HMGB1 alarmin in the induction of inflammation and immunity has also recently been demonstrated in the context of overcoming tolerance. It is known that the two types of cell death have distinct immunological outcomes: necrosis often results in inflammation and adaptive immunity, whereas apoptosis tends to be anti-inflammatory and promotes immune tolerance. In the course of investigating the features of apoptotic cells responsible for the induction of tolerance, Kazama and coworkers [112] found that the oxidization of HMGB1 by reactive oxygen species (ROS) generated in the course of apoptosis neutralizes the immunostimulatory activity of HMGB1 and consequently enables the tolerance-inducing capacity of apoptotic cells. Blockade of the ROS oxidization of HMGB1 during apoptosis converted the resulting apoptotic cells from tolerogenic into immunogenic inducers [112]. Therefore, suppressing the alarmin activity of HMGB1 in the course of apoptosis is critical for maintaining immune homeostasis and preventing unwanted adaptive immune responses against self antigen(s) associated with apoptotic cells. Feed-back

inhibitory pathway that downregulates HMGB1 effects has also been identified. Chen and coworkers [113] found that the interaction of CD24 with the Siglec (sialic acid-binding immunoglobulin-like lectin) -G (or Siglec-10 in humans) receptor dampened the innate/inflammatory response elicited by HMGB1 released from acetaminophen (AAP)-damaged hepatocytes. Initially, they observed that CD24 knockout mice died rapidly in response to sublethal dose of AAP treatment, which was accompanied by a massive increase in the inflammatory cytokines (TNF α , IL-6, and MCP-1) in the mouse serum [113]. Both HMGB1 and Siglec-G were identified as CD24-binding partners [113]. They concluded that AAP treatment resulted in the release of HMGB1 that, in turn, led to inflammation by triggering the inflammatory cytokine production by DCs, which was dampened by CD24-Siglec-G-mediated inhibition of HMGB1-induced NF- κ B activation in DCs [113]. Furthermore, AAP-induced sterile inflammation could also be exacerbated by knockout of Siglec-G or inhibited by treatment of experimental mice with HMGB1-neutralizing antibody. Interestingly, CD24- or Siglec-G-knockout mice did not show any increase in susceptibility to endotoxin-induced lethality or production of inflammatory cytokines [113], suggesting that CD24-Siglec-G regulatory circuit has perhaps evolved to selectively dampen inflammation induced by alarmins/DAMPs, but not by PAMPs. These observations provide additional evidence to support the importance of HMGB1 in the augmentation of innate/inflammatory and adaptive immune responses.

6. The alarmin properties of HMGN1

For a molecule to act as an alarmin, it has to be released extracellularly in order to act on APCs. HMGN2 was shown to be present in the culture supernatant of activated human peripheral blood mononuclear cells [18], suggesting that members of the HMGN family can also be released extracellularly. In collaboration with Bustin and colleagues, we have investigated the effect of HMGN1 and HMGN2 on the activation and recruitment of DCs. This revealed that HMGN1, but not HMGN2, had the capacity to induce phenotypic and functional maturation of DCs. In addition, HMGN1 induced the *in vivo* recruitment of DCs into sites of HMGN1 administration. Additional experiments demonstrated that HMGN1 was able to enhance *in vivo* antigen-specific immune responses. Therefore, HMGN1 also acts as an alarmin based on its DC-recruiting and activating properties as well as its capacity to enhance adaptive immune responses. The contribution of HMGN1 to the induction of adaptive immunity was revealed by a remarkable reduction in antigen-specific immune responses in HMGN1 knockout mice in comparison with HMGN1 wild-type control mice. Consequently, HMGN1 is not redundant with HMGB1 for its alarmin functions.

7. Concluding remarks

Thus far, two members of the HMG superfamily of nuclear proteins have been identified as having an extracellular cytokine-like role as alarmins. It is of interest that some members of the IL-1 cytokine superfamily, in particular the precursors of IL-1 α and IL-33 (ProIL-1 α and ProIL-33), have also been shown to act as nuclear binding factors involved in the regulation of gene transcription [114,115]. Like HMGB1, IL-1 α and IL-33 are not secreted via the conventional ERGolgi pathway, but are exported following a process termed unconventional protein secretion [114,116]. IL-1 α is stored in many types of cells (e.g.

epithelial cells, fibroblast, endothelial cells, etc), and can also be induced by a variety of PAMPs and other cytokines [114,115]. IL-1 α does have the capacity to induce inflammatory reactions at injection sites, induces the maturation of DCs, and has adjuvant activity [115]. Therefore, IL-1 α is another nuclear factor that has most of the activities of an alarmin. Consequently, although first identified as cytokines and subsequently as nuclear factors, IL-1 α and perhaps IL-33 resembles HMGB1 and HMGN1 in having both intra-nuclear and extracellular activities. These molecules have evolved and developed the ability to act both as nuclear factors for the regulation of gene transcription and to contribute to the induction of innate and adaptive immune responses by activating membrane receptor-mediated signal transduction pathways. The combination of transcriptional and extracellular capabilities provides them with the dual capacity of promoting gene expression and mobilizing host defense. Unless they are generated to excess in response to major damage, they normally would help mobilize host defense in response to danger and restore homeostasis by promoting repair of damaged tissues. Overall, both HMGB1 and HMGN1 therefore have pivotal biological functions in development, host defense, and tissue repair independent of their direct effect on chromatin remodeling and gene transcription.

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Table 1

Effects of extracellular HMGB1 and HMGN1 on cells of the immune system.

Target cells	Biological effects	
	HMGB1	HMGN1
Epithelial cells/keratinocytes	Migration/chemotaxis promotion of wound healing	Not determined
Endothelial cells	Proangiogenic activation	Not determined
Neutrophils	Recruitment prevention of apoptosis	Not determined
Monocytes/macrophages	Promotion of migration activation	Activation
Dendritic cells	Migration/chemotaxis recruitment and homing maturation	Recruitment maturation
B lymphocytes	Activation	Not determined
T lymphocytes	Promotion of T cell proliferation	Activation