Biochemical and Biophysical Research Communications 450 (2014) 851–856

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

HMGB1–DNA complex-induced autophagy limits AIM2 inflammasome activation through RAGE

Liying Liu [a,b], Minghua Yang [b], Rui Kang [c], Yunpeng Dai [a], Yan Yu [b,c], Fei Gao [a], Hongmei Wang [a], Xiaojun Sun [a], Xiuli Li [a], Jianhua Li [d], Haichao Wang [d], Lizhi Cao [b,*], Daolin Tang [c,*]

[a] Department of Pediatrics, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong 250021, China
[b] Department of Pediatrics, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China
[c] Department of Surgery, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15219, USA
[d] The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030, USA

ARTICLE INFO

Article history:
Received 8 June 2014
Available online 24 June 2014

Keywords:
Inflammasome
Autophagy
HMGB1
RAGE
AIM2
DNA

ABSTRACT

High mobility group box 1 (HMGB1) is a prototype damage-associated molecular pattern (DAMP) that can induce inflammatory and immune responses alone as well as in combination with other molecules such as DNA. However, the intricate molecular mechanisms underlying HMGB1–DNA complex-mediated innate immune response remains largely elusive. In this study, we demonstrated that HMGB1–DNA complex initially induced absent in melanoma 2 (AIM2)-dependent inflammasome activation, and promoted rapid release of inflammasome-dependent early proinflammatory cytokines such as interleukin 1β (IL-1β). Subsequently, HMGB1–DNA complex stimulated an ATG5-dependent cellular degradation process, autophagy, which was paralleled by a cessation of AIM2 inflammasome activation and IL-1β release. These HMGB1–DNA complex-induced inflammasome activation and autophagy were both dependent on the receptor for advanced glycation endproducts (RAGE) that recognizes a wide array of ligands (including HMGB1 and DNA). Thus, autophagy may function as a negative counter-regulatory mechanism for HMGB1–DNA complex-induced inflammasome activation, and provide a checkpoint to limit the development of inflammation.

1. Introduction

Damage-associated molecular patterns (DAMPs) are host-derived molecules released from dead, dying, or injured cells. They mediate both immunogenic and tolerogenic cell death, and participate in the regulation of the innate immune response [1,2]. Although the list of DAMPs is growing, high mobility group box 1 (HMGB1) is the most widely-studied and best characterized DAMP. HMGB1 is structurally composed of two DNA-binding domains (box A and box B) and an acidic tail modulating DNA binding. HMGB1 is normally present in the nucleus and acts as an architectural protein with DNA binding and bending activity, which plays a specific role in sustaining chromatin structure and function. However, HMGB1 can translocate from the nucleus to the cytosol and then release to the extracellular space in an active or passive manner [3,4]. Once released, HMGB1 selectively binds to various receptors (e.g., receptor for advanced glycation endproducts [RAGE] and Toll-like receptors [TLRs]) in different cells, and mediates inflammatory responses either by itself or in combination with other molecules [5,6]. In particular, extracellular HMGB1 can bind to various types of DNA, including host genomic, mitochondrial, and microbial DNA, to form a complex to enhance the innate immune response to nucleic acids [7–9]. However, the molecular mechanisms underlying the HMGB1–DNA complex-mediated innate immune response still remains largely elusive.

Inflammasomes are innate inflammatory protein complexes of pro-caspase 1, adaptor proteins (e.g., apoptosis-associated speck-like protein containing a CARD, ASC) and a member of the PYHIN family (e.g., the absent in melanoma 2, AIM2). The assembly of

Abbreviations: AIM2, absent in melanoma 2; DAMP, damage-associated molecular pattern; DAI, DNA-dependent activator of IFN-regulatory factors; dsDNA, synthetic double-stranded DNA; HMGB1, high mobility group box 1; IL-1β, interleukin 1β; LRRFIP1, leucine-rich repeat (in FLII) interacting protein 1; LC3, microtubule-associated protein 1 light chain 3; PAMP, pathogen-associated molecular pattern molecule; RAGE, the receptor for advanced glycation endproducts; shRNA, short hairpin RNA; TLR, Toll-like receptor.

* Corresponding authors. Address: Department of Pediatrics, Xiangya Hospital, Central South University, 110 Xiangya Road Changsha, Hunan 410008, China. Fax: +86 731 84327922 (L. Cao). Address: G.27C, Hillman Cancer Center, 5117 Centre Ave, Pittsburgh, PA 15213, USA. Fax: +1 412 623 1212 (D. Tang).

E-mail addresses: lizhicao@gmail.com (L. Cao), tangd2@upmc.edu (D. Tang).

http://dx.doi.org/10.1016/j.bbrc.2014.06.074
0006-291X/

inflammasome enables the activation of caspase-1 and the production of interleukin 1β (IL-1β), an important proinflammatory cytokine in human disease [10]. Carrying two oligonucleotide-binding domains, AIM2 can function as a DNA sensor and activate inflammasome in response to cytoplasmic DNA [11,12]. In this study, we describe a novel regulatory mechanism for the HMGB1–DNA complex-mediated innate immune response. We demonstrated that HMGB1–DNA complex initially induced AIM2-dependent inflammasome activation and IL-1β release, and subsequently stimulated ATG5-dependent autophagy. Although both processes were dependent on the availability of RAGE, the subsequent autophagy may function as a negative counter-regulatory mechanism for the initial inflammasome activation, and provide a checkpoint to limit the development of inflammation.

2. Methods

2.1. Reagents

The antibodies to DNA-dependent activator of IFN-regulatory factors (DAI), leucine-rich repeat (in FLII) interacting protein 1 (LRRFIP1), AIM2, TLR4, and RAGE were obtained from Abcam (Cambridge, MA, USA). The antibodies to actin, microtubule-associated protein 1 light chain 3 (LC3), and ATG5 were obtained from Cell Signaling Technology (Danvers, MA, USA). Poly(dA:dT)/LyoVec™ was obtained from InvivoGen (San Diego, CA, USA). High purity recombinant HMGB1 protein was generated as previously described [13].

2.2. Cell culture

THP-1 and HL-60 cell lines were obtained from ATCC and cultured in RPMI-1640 Medium or Iscove's Modified Dulbecco's Medium (Life Technologies, USA) with 10% heat-inactivated FBS, 2 mM glutamine, and antibiotic-antimycotic mix in a humidified incubator with 5% CO_2 and 95% air.

2.3. Measurement of IL-1β release

IL-1β released into cell culture supernatants was evaluated using an enzyme-linked immunoabsorbent assay (ELISA) kit from R&D Systems, Inc. (Minneapolis, MN, USA) according to the manufacturer's instructions.

2.4. Measurement of caspase 1 activation

Caspase 1 activation in cell lysis was evaluated using a Caspase 1 Assay Kit (Colorimetric) from Abcam according to the manufacturer's instructions. The assay is based on spectrophotometric detection of the chromophore p-nitroanilide (p-NA) after cleavage from the labeled substrate YVAD-p-NA.

2.5. RNAi

Short hairpin RNA (shRNA) against human DAI, LRRFIP1, AIM2, ATG5, TLR4, and RAGE were obtained from Sigma (St. Louis, MO, USA) and were transfected into cells using lentiviral-mediated transfection (Sigma) according to the manufacturer's instructions. Detection of knockdown was assayed by Western blot.

2.6. Western blotting analysis

Cells were lysed in 20 mM Tris (pH 7.5), 150 mM NaCl, 1 mM EDTA, and 1% NP40 supplemented with a protease inhibitor (Complete Mini EDTA-free; Roche, Indianapolis, IN, USA) and phosphatase inhibitor mixture II (Sigma) [14]. Thirty micrograms of protein per lane was run on a denaturing 10% SDS–PAGE gel and subsequently transferred to polyvinylidene fluoride membranes via semidry transfer. After blocking the membrane at room temperature for 3 h, the membrane was incubated overnight at 4 °C with various primary antibodies. After incubation with peroxidase-conjugated secondary antibodies for 1 h at 25 °C, the signals were visualized using enhanced chemiluminescence (Pierce, Rockford, IL, USA).

2.7. Statistical analysis

Data are expressed as means ± SD. Significance of differences between groups was determined by two-tailed Student's t test or ANOVA LSD test. A p-value < 0.05 was considered significant.

3. Results

3.1. HMGB1 enhances DNA-induced inflammasome activation in human monocytic cells

Poly(dA:dT), a repetitive synthetic double-stranded DNA (dsDNA) sequence of poly(dA-dT).poly(dT-dA), can trigger inflammasome-mediated IL-1β production [15]. Given that a previous study demonstrated that HMGB1 can directly bind to poly(dA:dT) *in vitro* [16], we therefore examined whether exogenous HMGB1 would affect poly(dA:dT)-induced caspase 1 activation and IL-1β release in human monocytic cells (THP-1 and HL-60). By itself, HMGB1 triggered significant caspase 1 activation and IL-1β release within 3 h only when given at high (5 μg/ml), but not low dose (200 ng/ml), doses (Fig. 1A and B). However, at low doses, HMGB1 significantly enhanced poly(dA:dT)-induced caspase 1 activation and IL-1β release within 3 h, but not anymore at a late stage (8–24 h) (Fig. 1A and B). Thus, there is a synergistic effect between low dose HMGB1 and dsDNA in triggering inflammasome activation and IL-1β release at an early stage.

3.2. AIM2 is required for HMGB1–DNA complex-mediated inflammasome activation

Poly(dA:dT) is recognized by several cytosolic DNA sensors, including DAI [17], LRRFIP1 [18], and AIM2 [15]. To determine whether all these cytosolic DNA sensors were responsible for HMGB1–DNA complex-mediated inflammasome activation, we transfected THP-1 cells with specific shRNA targeting DAI, LRRFIP1, or AIM2, respectively (Fig. 2A). The knockdown of AIM2, but not DAI or LRRFIP1, significantly impaired HMGB1–poly(dA:dT)-induced caspase 1 activation and IL-1β release in THP-1 cells (Fig. 2B). Similarly, the knockdown of AIM2 by shRNA in HL-60 cells (Fig. 2C) also inhibited HMGB1–poly(dA:dT)-induced caspase 1 activation and IL-1β release (Fig. 2D). Collectively, these findings suggest an essential role for AIM2 in HMGB1–DNA complex-mediated inflammasome activation.

3.3. RAGE is required for HMGB1–DNA complex-mediated inflammasome activation

HMGB1 is recognized by several cell surface receptors such as RAGE and TLR4 [5]. To determine which receptor is required for HMGB1–DNA complex-mediated inflammasome activation, we transfected THP-1 cells with specific shRNA targeting RAGE or TLR4, respectively (Fig. 3A). The knockdown of RAGE, but not TLR4, significantly attenuated HMGB1–poly(dA:dT)-induced caspase 1 activation and IL-1β release (Fig. 3B). Similarly, the suppression of RAGE expression by shRNA in HL-60 cells (Fig. 3C) also impaired HMGB1–poly(dA:dT)-induced caspase 1 activation and IL-1β release

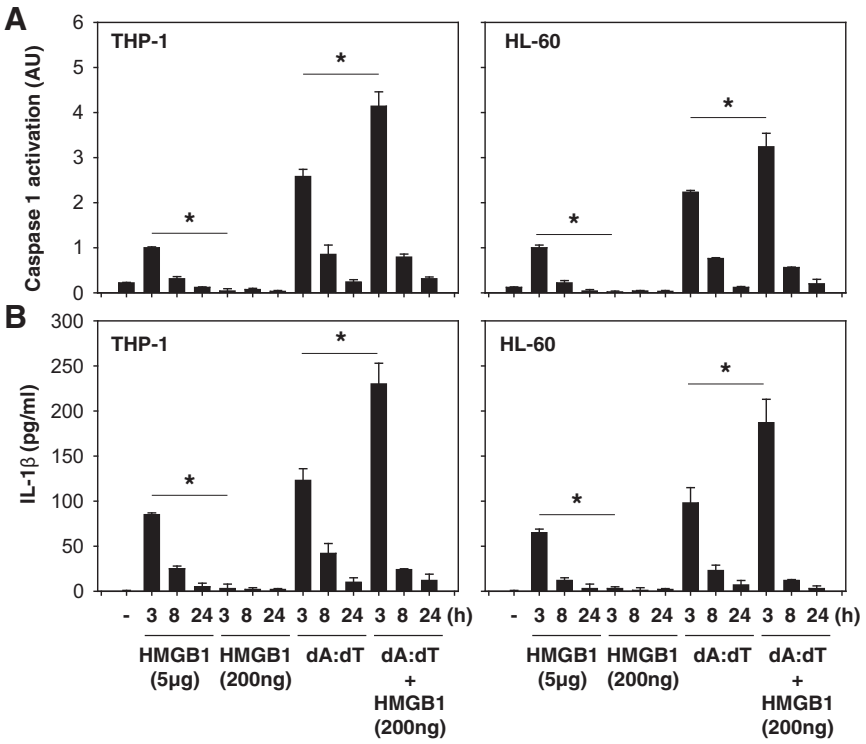

Fig. 1. HMGB1 enhances DNA-induced inflammasome activation in human monocytic cells. THP-1 and HL-60 cells were treated with HMGB1 (5 μg/ml or 200 ng/ml) in the absence and presence of 1 μg/ml Poly(dA:dT)/LyoVec™ for 3–24 h, and then caspase 1 activity (A) and IL-1β release (B) were analyzed as described in Section 2 ($n = 3$, $^*P < 0.05$). "AU": arbitrary units.

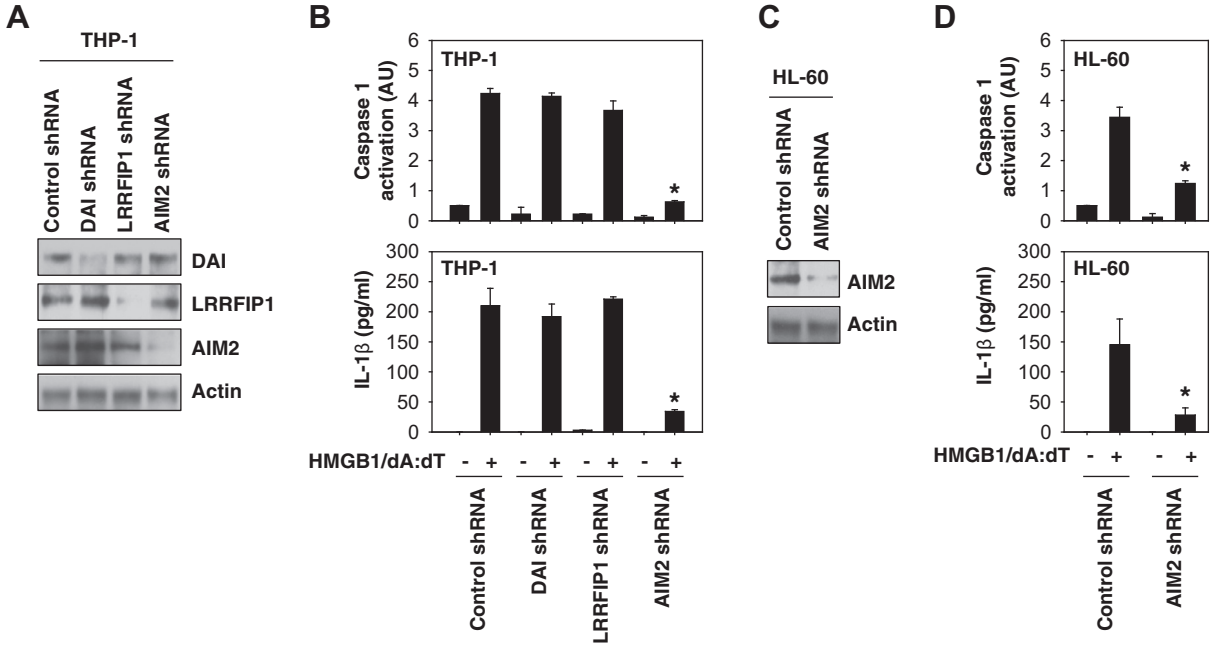

Fig. 2. AIM2 is required for HMGB1–DNA complex-mediated inflammasome activation. THP-1 (A and B) and HL-60 cells (C and D) were transfected with indicated shRNA for 48 h and then treated with HMGB1 (200 ng/ml) plus 1 μg/ml Poly(dA:dT)/LyoVec™ for 3 h ("HMGB1/dA:dT). Caspase 1 activity and IL-1β release (B and D) were analyzed as described in Section 2 ($n = 3$, $^*P < 0.05$ versus control shRNA group). "AU": arbitrary units.

(Fig. 3D). These findings suggest that RAGE is important for HMGB1–DNA complex-mediated inflammasome activation.

3.4. Autophagy limits HMGB1–DNA complex-mediated AIM2 inflammasome activation

Autophagy is generally a programmed survival mechanism in response to stress; however, excessive autophagy can cause cell death [19,20]. Autophagy can be measured by tracking the level of conversion of LC3-I to LC3-II. In particular, LC3-II levels correlate with autophagosome formation due to its association with the autophagosome membrane [21]. Consistent with our previous findings [22,23], we found that exogenous HMGB1 significantly increased LC3-II levels only at a late stage (24 h) and when given at a high dose (Fig. 4A). However, at relative low doses, HMGB1 enhanced poly(dA:dT)-mediated elevation of LC3-II production at

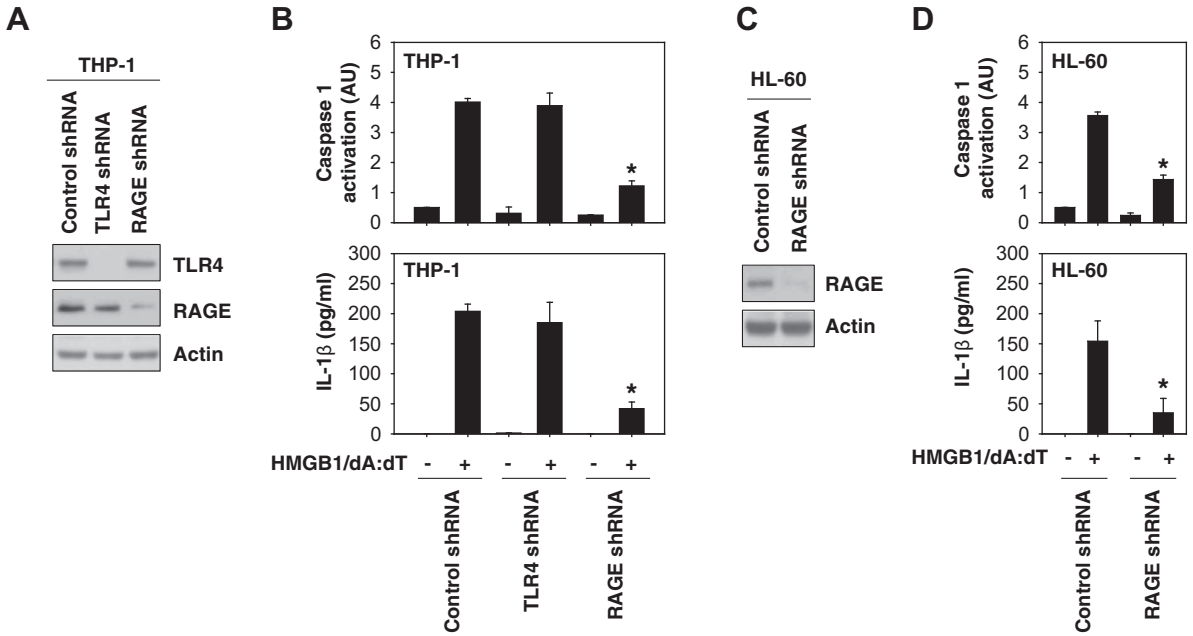

Fig. 3. RAGE is required for HMGB1–DNA complex-mediated inflammasome activation. THP-1 (A and B) and HL-60 cells (C and D) were transfected with indicated shRNA for 48 h and then treated with HMGB1 (200 ng/ml) plus 1 μg/ml Poly(dA:dT)/LyoVec™ for 3 h ("HMGB1/dA:dT"). Caspase 1 activity and IL-1β release (B and D) were analyzed as described in Section 2 ($n = 3$, $^*P < 0.05$ versus control shRNA group). "AU": arbitrary units.

24 h (Fig. 4A), suggesting a synergistic effect between low dose HMGB1 and dsDNA in triggering autophagy.

To understand the possible relationship between HMGB1–DNA complex-induced inflammasome activation and autophagy, we transfected THP1 cells with shRNA targeting key signaling molecules of these processes. The knockdown of AIM2 resulted in a reduction of IL-1β release (Fig. 2), but not LC3-II production, in response to HMGB1–DNA complex (Fig. 4B). In contrast, the knockdown of the autophagic regulator ATG5 inhibited LC3-II expression and prolonged IL-1β release to 24 h following stimulation with HMGB1–DNA complex (Fig. 4C). These findings suggest that the activation of autophagy at the late stage may limit the extent and timing of the HMGB1–DNA complex-mediated AIM2 inflammasome activation. This mechanism may explain why IL-1β release is only observed during an early stage of monocyte activation. In addition, we observed that the knockdown of RAGE impaired HMGB1–DNA complex-induced IL-1β release (Fig. 3) and LC3-II production (Fig. 4D), suggesting an important role for RAGE in HMGB1–DNA complex-induced inflammasome activation and autophagy (Fig. 4E).

4. Discussion

HMGB1 is a prototype DAMP that can induce inflammatory and immune responses by itself as well as in combination with other molecules [6]. Growing evidence has pointed to a correlative and causative relationship between serum HMGB1 and the development of many human diseases, including inflammatory, autoimmune, and neurodegenerative diseases and cancers [24,25]. Thus, it is important to understand the mechanism of HMGB1-mediated innate immune responses under pathophysiological conditions. In this study, we provided the first evidence that HMGB1–DNA complex can activate both injury (inflammasome) and anti-injury (autophagy) mechanisms in human monocytic cell lines. The activation of autophagy at the late stage may have limited the extent of HMGB1–DNA-mediated inflammasome activation and cytokine IL-1β release. These findings therefore identified a novel negative feedback regulatory mechanism for controlling HMGB1 activity in the innate immune response.

Inflammasomes are cytosolic multiprotein complexes that include an inflammasome sensor molecule, the adaptor protein ASC, and caspase 1. They play an important role in monitoring pathogen-associated molecular pattern molecules (PAMPs), DAMPs, or other cellular alarms, and activate programmed cellular immune responses such as caspase 1 activation and the release of pro-inflammatory cytokines (e.g., IL-1β) [10]. The concentrations of serum HMGB1 in patients can easily reach 200 ng/ml [26]. By itself, however, HMGB1 fails to trigger inflammasome activation when given at lower doses (200 ng/ml). If given at higher doses or in combination with DNA, HMGB1 can effectively stimulates AIM2-dependent inflammasome activation as manifested by increased caspase 1 activation and IL-1β release. These findings support the recent notion that pure recombinant HMGB1 has low or no immune activity and only acts as a DAMP when HMGB1 binds with other proteins or molecules [6]. It is not yet known whether HMGB1–DNA complex also promotes HMGB1 release through activating inflammasome, which has been suggested as a key regulatory mechanism of HMGB1 release [27,28]. If so, it would suggest cross-regulatory relationship between HMGB1 release and inflammasome activation in innate immune responses.

Recently, a large number of studies have suggested that both DAMPs and PAMPs can activate autophagy [29]; whereas dysregulated autophagy is linked to inflammation and immunity [30]. For instance, we have recently proposed HMGB1 as a positive regulator of autophagy, and HMGB1-mediated autophagy increases chemotherapy resistance in several tumors [22,23,31–33]. Consistently, the conditional knockout of HMGB1 in the pancreas, liver, or myeloid cells renders mice more sensitive to injurious [34,35] and infectious insults [36] partly through inhibition of autophagy [36] and upregulation of mitochondrial injury [35] and DNA damage [34]. Our current study now indicates that the induction of autophagic response may provide a negative feedback regulation of early inflammasome signaling elicited by HMGB1–DNA complex. This possibility is supported by previous reports that the impairment of autophagy promoted caspase 1 activation and release of inflammasome-dependent cytokines [37–39]. Indeed, autophagy can limit inflammasome activation at multiple levels [39–41] such as by eliminating damaged mitochondria (to prevent

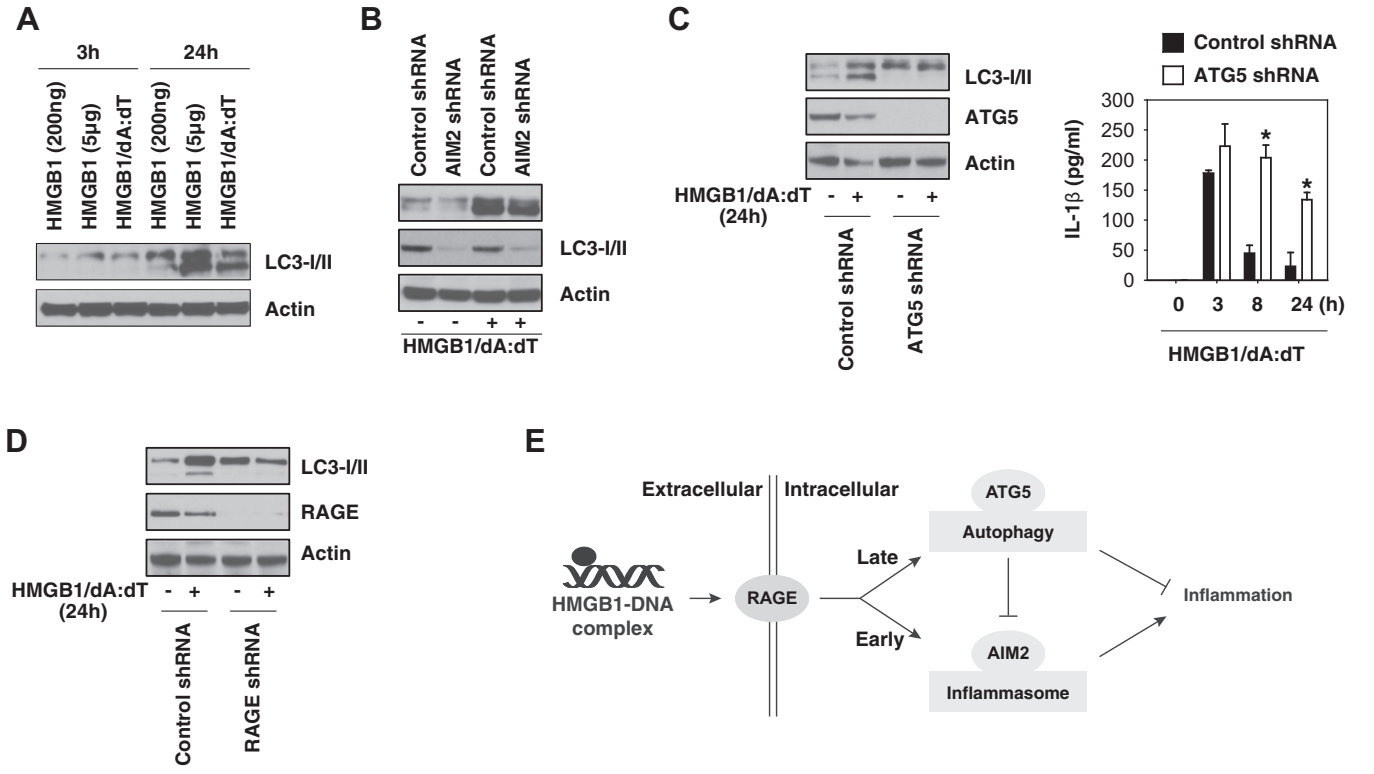

Fig. 4. Autophagy limits HMGB1–DNA complex-mediated AIM2 inflammasome activation. (A) Analysis of LC3 by Western blot in THP-1 cells after HMGB1 (200 ng/ml or 1 μg/ml) or HMGB1 (200 ng/ml) plus 1 μg/ml Poly(dA:dT)/LyoVec™ ("HMGB1/dA:dT) for 3–24 h. (B–D) After transfection with AIM2 shRNA (B), ATG5 shRNA (C), RAGE shRNA (D), or control shRNA for 48 h, cells were treated with HMGB1 (200 ng/ml) plus 1 μg/ml Poly(dA:dT)/LyoVec™ ("HMGB1/dA:dT) for 24 h. Total protein extracts were used for Western blot analysis. IL-1β release (C) was analyzed using ELISA ($n = 3$, $^*P < 0.05$ versus control shRNA group). (E) Schematic of the mechanism by which HMGB1–DNA complex modulates the inflammatory response by regulating inflammasome activation and the autophagic response at the early and late stages, respectively.

mitochondrial DNA release) [42], removing active inflammasomes [38][39], and destroying cytoplasmic HMGB1 [43,44]. Thus, autophagy dysfunction is causatively linked to the aberrant immune response, although the role of autophagy in inflammation and immunity is both dynamic and highly complex.

As a cell surface receptor for multiple ligands (including HMGB1 and DNA) [45], RAGE is involved in the initiation and propagation of inflammatory responses. Consistently, the genetic disruption of RAGE expression renders animals resistant to lethal systemic inflammatory insults such as sepsis [46]. Indeed, RAGE increases innate immune responses to HMGB1 and CpG-rich dsDNA [8], and is essential for the AIM2-dependent immune response to HMGB1 and poly(dA:dT) dsDNA. It has supported an exciting possibility that RAGE serves as a central receptor for innate recognition of HMGB1–DNA complexes.

In summary, our findings show that autophagy functions as a negative regulator of HMGB1–DNA-induced AIM2-dependent inflammasome activation. This work also reinforces the important role of RAGE in regulating the host response to extracellular HMGB1 and dsDNA.

Conflict of interest

The authors declare no conflicts of interest or financial interests.

Acknowledgments

We thank Christine Heiner (Department of Surgery, University of Pittsburgh) for her critical reading of the manuscript. This work was supported by grants from The National Natural Sciences Foundation of China (81200378 to L.L.; 31171328 and 81370648 to L.C.; 81270616 to Y.Y.; 81100359 to M.Y), the National Institutes of Health of USA (R01CA160417 to D.T.; R01AT005076 and R01GM063075 to H.W.) and a 2013 Pancreatic Cancer Action Network-AACR Career Development Award (Grant Number 13-20-25-TANG). This project used University of Pittsburgh Cancer Institute shared resources that are supported in part by award P30CA047904.

References

[1] W. Hou, Q. Zhang, Z. Yan, R. Chen, H.J. Zeh Iii, R. Kang, M.T. Lotze, D. Tang, Strange attractors: DAMPs and autophagy link tumor cell death and immunity, Cell death and disease 4 (2013) e966.
[2] L. Zitvogel, O. Kepp, G. Kroemer, Decoding cell death signals in inflammation and immunity, Cell 140 (2010) 798–804.
[3] H. Wang, O. Bloom, M. Zhang, J.M. Vishnubhakat, M. Ombrellino, J. Che, A. Frazier, H. Yang, S. Ivanova, L. Borovikova, K.R. Manogue, E. Faist, E. Abraham, J. Andersson, U. Andersson, P.E. Molina, N.N. Abumrad, A. Sama, K.J. Tracey, HMG-1 as a late mediator of endotoxin lethality in mice, Science 285 (1999) 248–251.
[4] P. Scaffidi, T. Misteli, M.E. Bianchi, Release of chromatin protein HMGB1 by necrotic cells triggers inflammation, Nature 418 (2002) 191–195.
[5] M.T. Lotze, K.J. Tracey, High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal, Nat. Rev. Immunol. 5 (2005) 331–342.
[6] M.E. Bianchi, HMGB1 loves company, J. Leukoc. Biol. 86 (2009) 573–576.
[7] S. Ivanov, A.M. Dragoi, X. Wang, C. Dallacosta, J. Louten, G. Musco, G. Sitia, G.S. Yap, Y. Wan, C.A. Biron, M.E. Bianchi, H. Wang, W.M. Chu, A novel role for HMGB1 in TLR9-mediated inflammatory responses to CpG-DNA, Blood (2007).
[8] J. Tian, A.M. Avalos, S.Y. Mao, B. Chen, K. Senthil, H. Wu, P. Parroche, S. Drabic, D. Golenbock, C. Sirois, J. Hua, L.L. An, L. Audoly, G. La Rosa, A. Bierhaus, P. Naworth, A. Marshak-Rothstein, M.K. Crow, K.A. Fitzgerald, E. Latz, P.A. Kiener, A.J. Coyle, Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE, Nat. Immunol. 8 (2007) 487–496.
[9] H. Yanai, T. Ban, Z. Wang, M.K. Choi, T. Kawamura, H. Negishi, M. Nakasato, Y. Lu, S. Hangai, R. Koshiba, D. Savitsky, L. Ronfani, S. Akira, M.E. Bianchi, K. Honda, T. Tamura, T. Kodama, T. Taniguchi, HMGB proteins function as universal sentinels for nucleic-acid-mediated innate immune responses, Nature 462 (2009) 99–103.
[10] K. Schroder, J. Tschopp, The inflammasomes, Cell 140 (2010) 821–832.

[11] T. Fernandes-Alnemri, J.W. Yu, P. Datta, J. Wu, E.S. Alnemri, AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA, Nature 458 (2009) 509–513.
[12] V.A. Rathinam, Z. Jiang, S.N. Waggoner, S. Sharma, L.E. Cole, L. Waggoner, S.K. Vanaja, B.G. Monks, S. Ganesan, E. Latz, V. Hornung, S.N. Vogel, E. Szomolanyi-Tsuda, K.A. Fitzgerald, The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses, Nat. Immunol. 11 (2010) 395–402.
[13] J. Li, R. Kokkola, S. Tabibzadeh, R. Yang, M. Ochani, X. Qiang, H.E. Harris, C.J. Czura, H. Wang, L. Ulloa, H.S. Warren, L.L. Moldawer, M.P. Fink, U. Andersson, K.J. Tracey, H. Yang, Structural basis for the proinflammatory cytokine activity of high mobility group box 1, Mol. Med. 9 (2003) 37–45.
[14] D. Tang, R. Kang, K.M. Livesey, C.W. Cheh, A. Farkas, P. Loughran, G. Hoppe, M.E. Bianchi, K.J. Tracey, H.J. Zeh 3rd, M.T. Lotze, Endogenous HMGB1 regulates autophagy, J. Cell Biol. 190 (2010) 881–892.
[15] V. Hornung, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D.R. Caffrey, E. Latz, K.A. Fitzgerald, AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, Nature 458 (2009) 514–518.
[16] S. Muller, M.E. Bianchi, S. Knapp, Thermodynamics of HMGB1 interaction with duplex DNA, Biochemistry 40 (2001) 10254–10261.
[17] A. Takaoka, Z. Wang, M.K. Choi, H. Yanai, H. Negishi, T. Ban, Y. Lu, M. Miyagishi, T. Kodama, K. Honda, Y. Ohba, T. Taniguchi, DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response, Nature 448 (2007) 501–505.
[18] P. Yang, H. An, X. Liu, M. Wen, Y. Zheng, Y. Rui, X. Cao, The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenin-dependent pathway, Nat. Immunol. 11 (2010) 487–494.
[19] G. Kroemer, G. Marino, B. Levine, Autophagy and the integrated stress response, Mol. Cell 40 (2010) 280–293.
[20] D.J. Klionsky, S.D. Emr, Autophagy as a regulated pathway of cellular degradation, Science 290 (2000) 1717–1721.
[21] Y. Kabeya, N. Mizushima, T. Ueno, A. Yamamoto, T. Kirisako, T. Noda, E. Kominami, Y. Ohsumi, T. Yoshimori, LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing, EMBO J. 19 (2000) 5720–5728.
[22] D. Tang, R. Kang, C.W. Cheh, K.M. Livesey, X. Liang, N.E. Schapiro, R. Benschop, L.J. Sparvero, A.A. Amoscato, K.J. Tracey, H.J. Zeh, M.T. Lotze, HMGB1 release and redox regulates autophagy and apoptosis in cancer cells, Oncogene 29 (2010) 5299–5310.
[23] L. Liu, M. Yang, R. Kang, Z. Wang, Y. Zhao, Y. Yu, M. Xie, X. Yin, K.M. Livesey, M.T. Lotze, D. Tang, L. Cao, HMGB1-induced autophagy promotes chemotherapy resistance in leukemia cells, Leukemia 25 (2011) 23–31.
[24] U. Andersson, K.J. Tracey, HMGB1 is a therapeutic target for sterile inflammation and infection, Annu. Rev. Immunol. 29 (2011) 139–162.
[25] R. Kang, Q. Zhang, H.J. Zeh 3rd, M.T. Lotze, D. Tang, HMGB1 in cancer: good, bad, or both?, Clin Cancer Res. 19 (2013) 4046–4057.
[26] D.C. Angus, L. Yang, L. Kong, J.A. Kellum, R.L. Delude, K.J. Tracey, L. Weissfeld, Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis*, Crit. Care Med. (2007).
[27] R. Kang, D. Tang, PKR-dependent inflammatory signals, Sci. Signal. 5 (2012) pe47.
[28] B. Lu, T. Nakamura, K. Inouye, J. Li, Y. Tang, P. Lundback, S.I. Valdes-Ferrer, P.S. Olofsson, T. Kalb, J. Roth, Y. Zou, H. Erlandsson-Harris, H. Yang, J.P. Ting, H. Wang, U. Andersson, D.J. Antoine, S.S. Chavan, G.S. Hotamisligil, K.J. Tracey, Novel role of PKR in inflammasome activation and HMGB1 release, Nature 488 (2012) 670–674.
[29] D. Tang, R. Kang, C.B. Coyne, H.J. Zeh, M.T. Lotze, PAMPs and DAMPs: signal 0s that spur autophagy and immunity, Immunol. Rev. 249 (2012) 158–175.
[30] B. Levine, N. Mizushima, H.W. Virgin, Autophagy in immunity and inflammation, Nature 469 (2011) 323–335.
[31] D. Tang, R. Kang, K.M. Livesey, H.J. Zeh 3rd, M.T. Lotze, High mobility group box 1 (HMGB1) activates an autophagic response to oxidative stress, Antioxid. Redox Signal. 15 (2011) 2185–2195.
[32] J. Huang, J. Ni, K. Liu, Y. Yu, M. Xie, R. Kang, P. Vernon, L. Cao, D. Tang, HMGB1 promotes drug resistance in osteosarcoma, Cancer Res. 72 (2012) 230–238.
[33] K.M. Livesey, R. Kang, P. Vernon, W. Buchser, P. Loughran, S.C. Watkins, L. Zhang, J.J. Manfredi, H.J. Zeh 3rd, L. Li, M.T. Lotze, D. Tang, P53/HMGB1 complexes regulate autophagy and apoptosis, Cancer Res. 72 (2012) 1996–2005.
[34] R. Kang, Q. Zhang, W. Hou, Z. Yan, R. Chen, J. Bonaroti, P. Bansal, T.R. Billiar, A. Tsung, Q. Wang, D.L. Bartlett, D.C. Whitcomb, E.B. Chang, X. Zhu, H. Wang, B. Lu, K.J. Tracey, L. Cao, X.G. Fan, M.T. Lotze, H.J. Zeh 3rd, D. Tang, Intracellular HMGB1 inhibits inflammatory nucleosome release and limits acute pancreatitis in mice, Gastroenterology (2013).
[35] H. Huang, G.W. Nace, K.A. McDonald, S. Tai, J.R. Klune, B.R. Rosborough, Q. Ding, P. Loughran, X. Zhu, D. Beer-Stolz, E.B. Chang, T. Billiar, A. Tsung, Hepatocyte specific HMGB1 deletion worsens the injury in liver ischemia/reperfusion: a role for intracellular HMGB1 in cellular protection, Hepatology (2013).
[36] H. Yanai, A. Matsuda, J. An, R. Koshiba, J. Nishio, H. Negishi, H. Ikushima, T. Onoe, H. Ohdan, N. Yoshida, T. Taniguchi, Conditional ablation of HMGB1 in mice reveals its protective function against endotoxemia and bacterial infection, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 20699–20704.
[37] T. Saitoh, N. Fujita, M.H. Jang, S. Uematsu, B.G. Yang, T. Satoh, H. Omori, T. Noda, N. Yamamoto, M. Komatsu, K. Tanaka, T. Kawai, T. Tsujimura, O. Takeuchi, T. Yoshimori, S. Akira, Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production, Nature 456 (2008) 264–268.
[38] K.G. Lassen, P. Kuballa, K.L. Conway, K.K. Patel, C.E. Becker, J.M. Peloquin, E.J. Villablanca, J.M. Norman, T.C. Liu, R.J. Heath, M.L. Becker, L. Fagbami, H. Horn, J. Mercer, O.H. Yilmaz, J.D. Jaffe, A.F. Shamji, A.K. Bhan, S.A. Carr, M.J. Daly, H.W. Virgin, S.L. Schreiber, T.S. Stappenbeck, R.J. Xavier, Atg16L1 T300A variant decreases selective autophagy resulting in altered cytokine signaling and decreased antibacterial defense, Proc. Natl. Acad. Sci. U.S.A. (2014).
[39] C.S. Shi, K. Shenderov, N.N. Huang, J. Kabat, M. Abu-Asab, K.A. Fitzgerald, A. Sher, J.H. Kehrl, Activation of autophagy by inflammatory signals limits IL-1beta production by targeting ubiquitinated inflammasomes for destruction, Nat. Immunol. 13 (2012) 255–263.
[40] N. Dupont, S. Jiang, M. Pilli, W. Ornatowski, D. Bhattacharya, V. Deretic, Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1beta, EMBO J. 30 (2011) 4701–4711.
[41] J. Harris, M. Hartman, C. Roche, S.G. Zeng, A. O'Shea, F.A. Sharp, E.M. Lambe, E.M. Creagh, D.T. Golenbock, J. Tschopp, H. Kornfeld, K.A. Fitzgerald, E.C. Lavelle, Autophagy controls IL-1beta secretion by targeting pro-IL-1beta for degradation, J. Biol. Chem. 286 (2011) 9587–9597.
[42] K. Nakahira, J.A. Haspel, V.A. Rathinam, S.J. Lee, T. Dolinay, H.C. Lam, J.A. Englert, M. Rabinovitch, M. Cernadas, H.P. Kim, K.A. Fitzgerald, S.W. Ryter, A.M. Choi, Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome, Nat. Immunol. 12 (2011) 222–230.
[43] Q. Zhang, R. Kang, H.J. Zeh 3rd, M.T. Lotze, D. Tang, DAMPs and autophagy: cellular adaptation to injury and unscheduled cell death, Autophagy 9 (2013) 451–458.
[44] W. Li, S. Zhu, J. Li, A. Assa, A. Jundoria, J. Xu, S. Fan, N.T. Eissa, K.J. Tracey, A.E. Sama, H. Wang, EGCG stimulates autophagy and reduces cytoplasmic HMGB1 levels in endotoxin-stimulated macrophages, Biochem. Pharmacol. 81 (2011) 1152–1163.
[45] C.M. Sirois, T. Jin, A.L. Miller, D. Bertheloot, H. Nakamura, G.L. Horvath, A. Mian, J. Jiang, J. Schrum, L. Bossaller, K. Pelka, N. Garbi, Y. Brewah, J. Tian, C. Chang, P.S. Chowdhury, G.P. Sims, R. Kolbeck, A.J. Coyle, A.A. Humbles, T.S. Xiao, E. Latz, RAGE is a nucleic acid receptor that promotes inflammatory responses to DNA, J. Exp. Med. 210 (2013) 2447–2463.
[46] B. Liliensiek, M.A. Weigand, A. Bierhaus, W. Nicklas, M. Kasper, S. Hofer, J. Plachky, H.J. Grone, F.C. Kurschus, A.M. Schmidt, S.D. Yan, E. Martin, E. Schleicher, D.M. Stern, G.G. Hammerling, P.P. Nawroth, B. Arnold, Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response, J. Clin. Invest. 113 (2004) 1641–1650.