The MTA1 coregulator, a component of the nucleosome remodeling and deacetylase (NuRD) complex, has been intimately linked with human cancer, but its role in inflammatory responses remains unknown. Here, we discovered that MTA1 is a target of inflammation, and depletion of MTA1 in LPS-stimulated macrophages impairs NF-κB signaling and transcription via the NF-κB signaling pathway. Unexpectedly, we found that MTA1 depletion in vivo causes increased mortality from septic shock, revealing that MTA1 protects mice from deregulated host inflammatory response. These findings reveal a previously unrecognized, critical homeostatic role of MTA1, both as a target and as a component of the NF-κB circuitry, in the regulation of inflammatory responses.

This article has been withdrawn by the authors. Upon becoming aware of concerns raised regarding errors with respect to Fig. 4B, the authors are withdrawing the paper and apologize for these errors. The senior author states that the experiments and the final assembly of Fig. 4B were performed by specific co-authors from his laboratory. The authors state that the potential issues raised with Fig. 4B do not affect the scientific conclusions of this work.

The inflammatory response is an integral part of the host defense mechanism against microbial agents that demands rapid and coordinated control of multiple inflammatory genes in immune cells, including macrophages. Early inflammatory response to microbial products such as lipopolysaccharide (LPS) activates the NF-κB signaling pathway (1); once activated, the NF-κB-p65/p50 heterodimer translocates to the nucleus, interacts with coregulatory molecules, recruits to the target promoters with the NF-κB consensus motif, and induces expression of the responsive genes (1). The NF-κB pathway is regulated at multiple levels by a series of transcriptional and post-translational events and may be involved in the dynamic coordinated participation of transcription factors in achieving gene transcription (5–11). Despite the presumptive significance of the regulatory mechanisms responsible for achieving coordinated and appropriate gene transcription, it is widely up-regulated in a wide variety of human tumors (14–15). MTA1, the first identified member of the MTA family of genes, regulates cellular pathways by associating and modifying the acetylation status of the target gene chromatin. MTA1 is a target of inflammation, and its depletion in LPS-stimulated macrophages impairs NF-κB signaling, revealing that MTA1 protects mice from deregulated host inflammatory response. These findings reveal a previously unrecognized, critical homeostatic role of MTA1, both as a target and as a component of the NF-κB circuitry, in the regulation of inflammatory responses.

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we provide evidence that MTA1 plays a critical homeostatic role in inflammatory responses both as a target and as a component of the NF-κB circuitry.

EXPERIMENTAL PROCEDURES

Antibodies and Cell Culture—Antibodies against MTA1 (A300-280A), MTA2 (A300-395A), MTA3 (A300–160A), and RNA polymerase II (pol II) (A300–653A) were purchased from Bethyl Laboratories (Montgomery, TX); and HDAC2 (catalog no. sc-9959), NF-κB p65 (p65) (catalog no. sc-372), phospho-NF-κB p65 (catalog no. sc-33020), NF-κB p50 (catalog no. sc-7178), phospho-NF-κB p50 (catalog no. sc-33022-R), and NF-κB p65 (catalog no. 286-H) X (catalog no. sc-7151 X) were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Phospho-IκBα (catalog no. 9241), phospho-IKKα/β (catalog no. 2697) were purchased from Cell Signaling Technology. Normal mouse IgG, rabbit IgG, and antibodies against actin and vinculin were purchased from Sigma. All cells were cultured in Dulbecco’s modified Eagle’s medium/F12 medium supplemented with 10% fetal bovine serum. HC11 cells were maintained in RPMI 1640 medium supplemented with 10% fetal calf serum, 10 ng/ml epidermal growth factor, and 5 μg/ml insulin.

Quantitative Real-time PCR Analysis—For quantitative real-time PCR (q-PCR), total RNA was extracted using TRIzol reagent (Invitrogen), and first-strand cDNA synthesis was carried out with SuperScript II reverse transcriptase (Invitrogen) using 2 μg of total RNA and poly(dT) primer. cDNA from all the genes were normalized to those of β-actin mRNA. The levels of mRNA of all the genes were normalized to those of β-actin mRNA. q-PCR was performed using a 7900HT sequence detection system (Applied Biosystems, Foster City, CA). The primers used are listed in supplemental Table 1. q-PCR was performed as described previously (20). For immunoprecipitation assays, 1 mg of cell lysates was incubated with MTA1 or pol II or HDAC2 or p65 antibody and agarose beads with constant rotation followed by extensive washing (20 mM HEPES (pH 7.6, 150 mM KCI, 1 mM dithiothreitol, 0.1% Nonidet P-40, and 8% glycerol). The immunoprecipitated proteins were resolved on SDS-PAGE, transferred to nitrocellulose membranes, and analyzed by Western blotting against NF-κB signaling components.

Isolation of Peritoneal Macrophage—After LPS treatment, peritoneal lavage was done with 10 ml of sterile ice-cold phosphate-buffered saline, and the peritoneal lavage fluid was collected. The cells were washed and resuspended in Dulbecco’s modified Eagle’s medium/F12 medium supplemented with 10% fetal bovine serum, cultured overnight, and then washed to remove nonadherent cells.

Immunoprecipitation and Immunoblot Analysis—Cell lysates were prepared in radioimmuneprecipitation assay lysis buffer, and Western blot analysis was performed as described previously (20). For immunoprecipitation assays, 1 mg of cell lysates was incubated with MTA1 or pol II or HDAC2 or p65 antibody and agarose beads with constant rotation followed by extensive washing (20 mM HEPES (pH 7.6, 150 mM KCl, 1 mM dithiothreitol, 0.1% Nonidet P-40, and 8% glycerol). The immunoprecipitated proteins were resolved on SDS-PAGE, transferred to nitrocellulose membranes, and analyzed by Western blotting against NF-κB signaling components.

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**RESULTS AND DISCUSSION**

**MTA1 Is an Inflammation-inducible Gene**—During an investigation involving treatment of primary murine peritoneal macrophages with *Escherichia coli* LPS, we discovered unexpectedly that LPS stimulation of macrophages results in a substantial induction of MTA1 mRNA but not MTA2 mRNA or MTA3 mRNA as measured by q-PCR (Fig. 1A). As expected, increased expressions of IL-1β, MIP2, IL-6, and TNF-α, the primary targets of LPS, were observed (Fig. 1A). The results suggest that *MTA1* may be an inflammation-inducible gene. Therefore, to test this hypothesis, we turned to LPS stimulation of Raw264.7 cell line (Raw cells), a widely used murine macrophage cell line, as a model system. We found that LPS stimulation led to increased expression of MTA1 protein (Fig. 1B) and mRNA as assessed by q-PCR (Fig. 1C). In contrast, LPS stimulation had no effect on the expression of MTA2 or MTA3 protein (Fig. 1B). Actinomycin-D, a transcriptional inhibitor, effectively blocked both LPS-inducible expression of MTA1 mRNA and protein (Fig. 1, C and D). These findings suggested that *MTA1* may be a target of inflammation.

**MTA1 Is an NF-κB-responsive Gene**—To directly test the notion that *MTA1* is an inflammation-inducible gene, we next cloned the putative murine *Mta1* promoter from mouse genomic DNA and generated a series of overlapping promoter fragments into a TATA-less, pGL3-luciferase (pGL3-luc) reporter system (supplemental Fig. 1A). We examined the inducibility of the *Mta1* promoter deletion constructs by TNF-α, the primary target of LPS (supplemental Fig. 1B). These experiments led to identification of the *Mta1* minimal promoter, which consisted of −2872 to −4770 relative to the presence of five NF-κB consensus motifs: GGAAAGCCAG (−2893 to −2872), GAGAGCTCCCA (−4761 to −4770), GAAAACGGTCCCC (−3967 to −3996), AGAGGCCCCACC (−3277 to −3295), and AAGAGGGGTCCTCATCAC (−3926 to −3935) (Fig. 2A). To understand the mechanism of LPS regulation of *MTA1* expression, we found that blocking the NF-κB pathway by either pharmacologic inhibitor parthenolide or IκBα-S12 (22), a specific dominant-negative mutant of IκB, effectively inhibited LPS-mediated stimulation of *Mta1* promoter activity in Raw cells (supplemental Fig. 2). As expected, LPS-mediated stimulation of *MTA1* mRNA expression was also inhibited by parthenolide (Fig. 2B).

To gain a deeper insight into LPS stimulation of *MTA1* transcription, we next used ChIP to examine the potential recruitment of p65 onto the *Mta1* promoter. Although the *Mta1* promoter contains five putative NF-κB consensus motifs (supplemental Fig. 1C), LPS stimulation resulted in enhanced recruitment of p65 only to region 1 (−4570 to −4889) (Fig. 2C) and not to regions 2 (−3814 to −4152) and 3 (−2874 to −3207) (Fig. 2C). In addition, we also found recruitment of pol II, a marker of stimulated chromatin, to this region (Fig. 2C). Interestingly, we also found a distinct derecruitment of HDAC2 from region 1 of the *Mta1* promoter upon LPS treatment (Fig. 2C). Similarly, p65+pol II complex was recruited only to region 1 of the *Mta1* promoter as revealed by sequential double ChIP studies (Fig. 2D).

To demonstrate the functionality of the responsible NF-κB motif in the *Mta1* promoter, we next mutated the NF-κB
motif in region 1 of the Mta1 promoter-luc reporter and showed that both LPS and p65 fail to stimulate the Mta1 promoter-luc activity containing a mutant NF-κB consensus motif (Fig. 2E). To demonstrate a potential direct binding of p65 to the mouse Mta1 promoter, we next performed EMSA using a 24-bp oligonucleotide encompassing the wild-type and mutant NF-κB consensus sequence of Mta1 promoter and nuclear extracts from Raw cells with or without LPS stimulation. As expected from the preceding results, LPS stimulation of Raw cells promoted higher levels of p65 DNA complex formation than those in the unstimulated Raw cells. The specificity of the noted complex was verified by supershift experiments using anti-p65 or control IgG (Fig. 2F, lanes 4–7) and by using MTA1 DNA probe with a defective NF-κB consensus sequence that did not interact with the cellular p65 (lanes 8–14). Together, these findings suggested that LPS stimulates MTA1 transcription via the NF-κB pathway and that MTA1 is an NF-κB-responsive gene.

MTA1 Is a Modifier of the LPS-inducible Genes in Stimulated Macrophage—We next examined the possibility that MTA1 is a new modifier of NF-κB signaling in LPS-stimulated macrophage. We found that selective siRNA-mediated knockdown of MTA1 in Raw cells impaired LPS-induced early activation of phospho-IKKα/β (Fig. 3A), IKKα/β kinase activity (Fig. 3B), and also delayed IκBα phosphorylation and p65 phosphorylation as compared with those observed in cells transfected with the con-
Regulation of NF-κB Circuitry Controls Homeostasis

We next examined whether MTA1 exerts a modifying function on NF-κB target genes in stimulated cells. We found that selective siRNA-mediated depletion of the endogenous MTA1 in Raw cells led to a significant fold reduction in LPS-induced expression of IL-1β, TNF-α, and MIP2 as compared with those of siRNA control cells (Fig. 4A and supplemental Fig. 3A). Consistent with these findings, MTA1 knockdown in Raw cells reduced the efficacy of LPS-induced transcription of IL-1β, TNF-α, and MIP2 from the basal level as compared with those in control siRNA-transfected cells, evaluated by the respective reporters (Fig. 4B and supplemental Fig. 3B). These findings implied that MTA1 may be important in achieving optimum induction of NF-κB target genes by LPS, suggesting that MTA1 may play a modifying role in the responsiveness of macrophages to LPS. To directly evaluate this possibility, we next examined the effect of ectopic MTA1 expression on LPS-mediated stimulation of IL-1β and TNF-α transcription using the respective promoter luc reporters (Fig. 4C). MTA1 overexpression was accompanied by increased levels of LPS-mediated stimulation of IL-1β and TNF-α expression in Raw cells as compared with vector-transfected control cells (Fig. 4D).

To further examine the potential comodifying role of MTA1 in LPS-mediated stimulation of the NF-κB target genes, we next examined whether LPS stimulation of macrophages also is accompanied by the recruitment of MTA1-pol II complex to NF-κB target gene promoters. Using a ChIP-based promoter walk, we first established that indeed, MTA1 is recruited to region 3 (−780 to −1211) of the IL-1β promoter, region 3 (−467 to −819) of the MIP2 promoter, and region 1 (−555 to −940) of the TNF-α promoter (Fig. 5, A–C). We observed that in Raw cells, LPS stimulation promoted recruitment of the MTA1-pol II complex to the IL-1β, TNF-α, and MIP2 promoters (Fig. 5D). Together, these results suggested that MTA1 behaves as a modifier of the LPS-inducible genes in the activated macrophages.
Revelation of Corepressor Activity of MTA1 on a Subset of NF-κB-Regulated Genes in Resting Cells—During the above studies, we consistently noticed that the knockdown in macrophages was accompanied by a decrease in the fold change of the levels of IL-1β, TNF-α, and MIP2 in type Raw cells (Fig. 4A). Moreover, in MTA1 knockdown cells, the mRNA basal levels of these NF-κB target genes and their basal promoter were not altered (supplemental Fig. 3). These findings support the possibility that MTA1 might act as a repressor of NF-κB target genes under basal, unstimulated conditions. Because MTA1 is part of the HDAC:NuRD corepressor complex, this hypothesis also was supported by our finding that LPS stimulation of macrophages was accompanied by derecruitment of the MTA1-HDAC2 corepressor complexes from the LPS-inducible NF-κB target gene chromatin: IL-1β, TNF-α, and MIP2 genes (Fig. 5E). Together, these results suggested that 1) MTA1 may repress the basal transcription of a subset of LPS-regulated target genes owing to a constitutive recruitment of the MTA1-HDAC2 complexes to the target promoter chromatin under unstimulated conditions and 2) MTA1 acts as a comodifier of a subset of NF-κB target genes in stimulated macrophages, probably owing to the release of HDAC2 from its target chromatin, probably, allowing the recruitment of pol II coactivator complexes to the target promoter chromatin. However, the precise nature of LPS-responsive components and associated protein modifications, which, in turn, might contribute to the noted recruitment of pol II coactivator complexes remains to be further investigated.

S-Nitrosylation of HDAC2 Abolishes Corepressor Activity of the MTA1-NuRD Complex—We next explored the notion that differential HDAC2 interaction with the NF-κB target gene chromatin during basal and LPS-inducible conditions may influence the status of MTA1 being a corepressor or loss of corepressor activity. We examined the effect of LPS stimulation on the relative interaction of MTA1 with HDAC2. We found that LPS stimulation of Raw cells led to a decreased interaction between MTA1 and HDAC2 in spite of increased expression of MTA1 by LPS (Fig. 6A). While this study was in progress, Nott et al. have shown that growth factor stimulation of nitric oxide (NO) production, via inducible nitric-oxide synthase, induces S-nitrosylation of nuclear HDAC2. Nitrosylated HDAC2, as a result, is released from the chromatin, leading to the loss of corepressor function and the stimulation of target gene transcription (23). In contrast, because inducible nitric oxide synthase also is an NF-κB target (24), we discovered that LPS stimulates S-nitrosylation of HDAC2 (Fig. 6B). Compare the nitrosylated HDAC2 modification could also stimulate a pharmacological inducible nitric-oxide synthase inhibitor L-NAME (Fig. 6B, compare lane 1 with lane 2). S-Nitrosylation of HDAC2 also reversed the loss of interaction between MTA1 and MTA1 in LPS-treated Raw cells (Fig. 6A). Consistent with the potential implication of S-nitrosylation of HDAC2 on the corepressor activity of the MTA1-HDAC2 complex, we found that LPS-mediated derecruitment of the MTA1-HDAC2 corepressor complex from the representative NF-κB target gene promoters such as IL-1β, TNF-α, and MIP2 promoters (Fig. 6C) could be effectively reversed by inducible nitric oxide synthase inhibitor L-NAME. To implicate these molecular changes with the functionality of the MTA1-HDAC2 corepressor complex, we showed that indeed, treatment of Raw cells with L-NAME, which prevents the release of MTA1-HDAC2 corepressor complex from IL-1β, TNF-α, and MIP2 promoters, also resulted in the failure in stimulating IL-1β, TNF-α, and MIP2-promoter activities by LPS (Fig. 6D) as well as expression of these LPS-inducible genes (Fig. 6E). Together, these findings suggest that the modulation of S-nitrosylation status of HDAC2 and its differential interaction with MTA1 in resting versus LPS-stimulated macrophages provides an explanation for the noted loss of corepressor behavior of MTA1 in activated macrophages.

MTA1 Modulation of Host Inflammatory and Septic Shock Responses—To confirm the possible differential effects of MTA1 knockdown under basal and LPS-stimulated conditions in a whole-animal setting, we used MTA1−/− mice, which were generated recently in our laboratory (25). We examined the levels of a subset of NF-κB target genes in cultured peritoneal macrophages from wild-type and MTA1−/− mice treated with E. coli LPS for 4 h. We found that MTA1 was consistent with our findings in vitro, because inducible nitric oxide synthase inhibitor L-NAME reversed the loss of corepressor behavior of MTA1 in activated macrophages.
Regulation of NF-κB Circuitry Controls Homeostasis

| Targets | MTA1 +/- | MTA1-/- | Fold increase |
|---------|----------|----------|---------------|
| IL-1β   | 14.7 ± 0.75 | 23.9 | 161±5.2 | 6.7 |
| MIP2    | 7.6 ± 0.50 | 2.77 | 4.31±1.0 | 1.55 |
| TNF-α   | 4.39 ± 1.52 | 23.0 | 85.6±2.5 | 3.72 |
| IL-6    | 15.1 ± 1.67 | 0.5 | 1.54±0.5 | 3.08 |

FIGURE 7. MTA1 modulation of host inflammatory and septic shock responses. A, q-PCR analysis of indicated genes (data presented are in fold change) in macrophages isolated from either wild-type or MTA1 knock-out (MTA1−/−) mice treated with LPS for 2 h. B, survival rates of mice in high injection of LPS (10 mg/kg) (n = 5 each group). C, estimation of TNF-α levels in circulation of wild-type and MTA1−/− mice before and after 2 h of LPS treatment by enzyme-linked immunosorbent assay. D, mice showing significant difference in the base level body temperature as compared with those of wild-type mice (n = 19/group). E, effect of LPS on the body temperature of wild-type and MTA1−/− mice. Data are shown as mean ± S.D.

FIGURE 8. Working Model. A, repression of a subset of proinflammatory cytokines by the MTA1-HDAC2 corepressor complex in the resting macrophages. B, transcriptional stimulation of MTA1 expression by the NF-κB pathway in LPS-stimulated macrophages. LPS enhances S-nitrosylation of HDAC2, leading to its dissociation from the MTA1-HDAC2 complex as well as from the target promoter; this, in turn, facilitates comodifying role of MTA1 on the expression of a subset of NF-κB genes. TLR, Toll-like receptor; S-NO, S-nitrosylation.

deficiency led to increased basal expression of the proinflammatory cytokines IL-1β, TNF-α, and MIP2 but not the anti-inflammatory cytokine IL-6, presumably due to the loss of MTA1-associated corepressor function (Fig. 7A). As expected, LPS stimulation induced the expression of NF-κB target genes in both wild-type and MTA1−/− mice. The stimulation levels, however, appeared to be dramatic in macrophages derived from MTA1−/− mice. Nevertheless, because the basal levels of NF-κB target genes were elevated in MTA1−/− macrophages compared with those of wild-type ones, fold change in cytokines expression between stimulated and basal in MTA1−/− macrophages were significantly lower than those of wild-type (Fig. 7A). Although these results apparently are paradoxical, they nevertheless are consistent with the findings in Raw cells and support the notion that MTA1 acts as a corepressor of a subset of the NF-κB target genes under basal conditions but acts as a modifier of the some of these genes in LPS-stimulated macrophages, suggesting a contribution of LPS-induced signals in the noted reversal of the basal corepressor activity.

To understand the impact of MTA1 deficiency on inflammatory responses, we examined the comparative susceptibility of MTA1−/− mice and wild-type mice to septic shock induced by E. coli LPS. Consistent with the findings of dramatic inflammatory response and increased expression of proinflammatory cytokines that mediates innate immune response, we observed a high rate of pronounced death of MTA1−/− mice within the first 40 h, whereas the wild-type mice survived during this period (Fig. 7B), presumably due to extremely high levels of circulating TNF-α, at least as one of the mechanisms (Fig. 7C), revealing a maintenance role of MTA1 in inflammatory response. As expected given the increased baseline expression of cytokines in macrophages from MTA1−/− mice (Fig. 7A), the normal body temperature of MTA1−/− mice was ~1 °C lower than the normal body temperature of the wild-type mice (Fig. 7D). Interestingly, LPS-induced septic shock triggered a further severe and lasting hypothermia in the MTA1−/− mice (body temperatures dropped to 27.3 °C), whereas in the wild-type mice, body temperature dropped to only 29 °C. However, the temperature returned to near the starting normal body temperature of 34 °C after LPS-induced decrease in body temperate in the wild-type animals (Fig. 7E). These findings suggested that MTA1 levels may provide an inherent protection in mice from deregulated host inflammatory response under conditions of septic shock and bacterial infection.

In summary, the results presented here have identified a critical role of MTA1, both as a target and as a modifier of the
NF-κB pathway, in conferring an optimal, sufficient inflammatory response against bacterial infection. As a mechanism of MTA1 regulation of a subset of LPS-inducible proinflammatory cytokines, the MTA1-HDAC2 corepressor complex differentially interacts with and remodels the target gene chromatin under basal and LPS-stimulated conditions (Fig. 8). As a result, the noted regulation of MTA1 by inflammation and the impact of MTA1 on NF-κB signaling and NF-κB target gene chromatin remodeling most likely are involved in the overall outcome of NF-κB signaling in macrophages. In conclusion, the findings presented here have identified a new regulatory layer of NF-κB signaling during inflammation and indicate that MTA1 represents as a player in and modifier to the NF-κB signaling network to, having a role in maintaining the homeostasis of inflammatory responses.

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