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Suppression of caspase-11 expression by histone deacetylase inhibitors

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ABSTRACT

It has been well documented that histone deacetylase inhibitors suppress inflammatory gene expression. Therefore, we investigated whether histone deacetylase inhibitors modulate the expression of caspase-11 that is known as an inducible caspase regulating both inflammation and apoptosis. In the present study, we show that sodium butyrate and trichostatin A, two structurally unrelated inhibitors of histone deacetylase (HDAC), effectively suppressed the induction of caspase-11 in mouse embryonic fibroblasts stimulated with lipopolysaccharides. Sodium butyrate inhibited the activation of upstream signaling events for the caspase-11 induction such as activation of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, degradation of inhibitor of κB, and activation of nuclear factor-κB. These results suggest that the HDAC inhibitor suppressed cytosolic signaling events for the induction of caspase-11 by inhibiting the deacetylation of non-histone proteins.

Recently histone deacetylase (HDAC) inhibitors have been paid much attention for their possible use as therapeutic drugs for cancer and inflammatory diseases [1,2]. Depending on the gene types or cellular context, HDAC inhibitors up- or down-regulate the expression of many genes important for the carcinogenesis or inflammation [3,4]. By activating the genes regulating cell cycle, differentiation, or apoptosis, HDAC inhibitors have been known to suppress tumorigenesis [1,3]. In general, histone acetylation enhances gene expression and the activation of many anticancer-related genes by HDAC inhibitors was found to be mediated by the chromatin remodeling caused by histone modification [5]. However, many genes are also repressed by HDAC inhibitors. Pro-inflammatory genes such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interferon-γ (IFN-γ), and inducible nitric oxide synthase (iNOS) have been shown to be down-regulated by the HDAC inhibitors in many cell types [2,3,6,7]. The repression of the proinflammatory genes has been suggested as a result of inhibition of nuclear factor-κB (NF-κB) activation and the acetylation of non-histone proteins [8–10]. However, the outcome and molecular pathway of the pharmacological inhibition of HDAC in inflammation vary or even contradict with each other depending on the cell type and the nature of stimuli [6,8–13]. Regardless of this unresolved molecular mechanism, many studies reported that the HDAC inhibitors exhibited fairly good anti-inflammatory effects in various *in vivo* models of inflammatory diseases such as rheumatoid arthritis [14,15], multiple sclerosis [16], septic shock [17], inflammatory bowel disease [18], and systemic lupus erythematosus [19]. More information on the mechanism of anti-inflammatory action will aid the effort to initiate clinical trials of the HDAC inhibitors for the treatment of inflammatory diseases.

Caspase-11 is a murine caspase known to regulate both apoptosis and inflammation in many disease models like septic shock, brain ischemia, experimental autoimmune encephalomyelitis, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease, and spinal cord injury [20–24]. Unlike other caspases, the expression of caspase-11 is tightly regulated at a transcriptional level [25,26]. Signaling mechanism of caspase-11 induction has been studied where the caspase-11 is induced by proinflammatory molecules like lipopolysaccharides (LPS) or IFN-γ [26–28]. LPS was shown to induce caspase-11 via toll-like receptor 4 (TLR4) signaling leading to NF-κB activation in primary microglial cells [28] and IFN-γ, by signal transducers and activators of transcription 1 (STAT1) in Mf4/4 macrophages [26]. Although the signaling event was not delineated, involvement of p38 MAPK and C/EBP homologous protein (CHOP) in the induction of caspase-11 was also reported in C6 rat glial cells and in mice, respectively [27,29]. Following induction, caspase-11 can physically interact with and activate caspase-1 [20]. By activating caspase-1, caspase-11 can regulate the maturation of pro-IL-1β and pro-IL-18 and thus regulate inflammatory response [20]. On the other hand, in certain pathological conditions, caspase-11 can activate caspase-3 and thus regulate apoptosis [21,23,30]. Since caspase-11 is inducible and involved in many disease conditions accompanying cell death and inflammation, pharmacological inhibitor of caspase-11 induction will be of great value to design anti-inflammatory therapy.

In the present study, we show that sodium butyrate and trichostatin A (TSA), two structurally unrelated inhibitors of HDAC,

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suppressed the induction of caspase-11 in the mouse embryonic fibroblasts (MEFs) following LPS stimulation. We also present evidence that the inhibition of caspase-11 is possibly mediated by modulation of non-histone proteins.

Materials and methods

Reagents. Anti-caspase-11 antibodies were described previously [25]. All of the primary antibodies were purchased form Cell signaling. All of the secondary antibodies and streptavidin conjugated with fluorophore were purchased from Jackson ImmunoResearch. IFN-γ was from Millipore. SB202190, SB203580, and SP600125 were from Calbiochem. All other antibodies and reagents were purchased from Sigma–Aldrich unless otherwise stated.

MEF culture. Following removal of head, limbs, and internal organs from d13 gestation ICR mouse embryos, the remaining tissues were dissociated by trypsinization and trituration with 0.1% trypsin–EDTA solution. The dissociated cells were resuspended in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin and anti-mycotics solution in a 37 °C CO_2 (5%) incubator.

RT-PCR. Total RNA from the MEFs was isolated using RNeasy minikit (Qiagen). cDNA was synthesized using the Moloney Murine Leukemia Virus Reverse Transcriptase (Promega) according to the manufacturer's protocol. The primers used for PCR are as follows: 5′-AGAAGTCTTACGGAGTACC-3′ (forward) and 5′-TGGTGTTCTGA GAGTGCAGC-3′ (reverse) for caspase-11; 5′-GAAAGCATGATCCGCG ACGTGG-3′ (forward) and 5′-GTAGACCTGCCCGGACTCCGCAA-3′ (reverse) for TNF-α. Mouse β-actin RT-PCR primer set was purchased from Stratagene. The caspase-11 and TNF-α primer pairs produced 550 and 650 bp PCR products, respectively. PCR consisted of an initial denaturation cycle at 94 °C for 2 min, followed by 27 cycles at 94 °C for 1 min, annealing at 52 or 54 °C for 1 min, and elongation at 72 °C for 1 min.

Immunoblots. MEFs (5×10^5/ml) grown on 60 mm dish were washed with cold PBS and lysed by incubation in 2× SDS sample buffer and boiled at 95 °C for 5 min. For the detection of phosphorylated proteins, Na_3VO_4 (1 mM) plus NaF (1 mM) were added in the washing and lysis buffers. Thirty to 40 micrograms of total protein was subjected to 10% SDS–polyacrylamide gel electrophoresis. Subsequent transfer and blotting were performed by conventional method.

Immunocytochemistry. Drug-treated MEFs were fixed in 4% paraformaldehyde in PBS, followed by a permeabilization with 0.2% Triton X-100 in PBS for 15 min. Subsequent blocking and antibody incubations were performed by conventional methods. Samples were examined under a fluorescence microscope (Axioplan 2, Zeiss).

Results and discussion

HDAC inhibitors suppressed the expression of caspase-11

Many studies have shown that HDAC inhibitors exhibit anti-inflammatory effects by suppressing the induction of cytokines like TNF-α, IL-1β, and IFN-γ [2,3,6,7]. Since caspase-11 is an inducible proinflammatory caspase regulating the maturation of cytokines like IL-1β and IL-18 [20,25], we hypothesized that HDAC inhibitors may suppress the induction of caspase-11 as well. To examine whether HDAC inhibitors indeed suppress the caspase-11 induction, MEFs were stimulated with LPS following 1 h pretreatment with HDAC inhibitor sodium butyrate or trichostatin A and then the expression level of caspase-11 was examined by immunoblot or RT-PCR analysis. As shown in Fig. 1A, sodium butyrate suppressed the induction of caspase-11 at both mRNA and protein levels. In accordance with the previous reports [2,6], the LPS-mediated induction of TNF-α was also suppressed by pretreatment with sodium butyrate (Fig. 1A). TSA, a structurally unrelated inhibitor of HDAC, also suppressed the induction of caspase-11 following LPS stimulation (Fig. 1B). However, the level of caspase-1 was not affected by the TSA treatment. These results show that the HDAC inhibitors that can suppress the induction of proinflammatory cytokines also suppress the induction of caspase-11 that is a regulator of proinflammatory cytokine maturation.

In a previous report, Kim et al. reported that sodium butyrate suppressed IFN-γ-, but not LPS-mediated induction of iNOS and TNF-α in microglia [13]. However, our result (Fig. 1A) and others' [2,6] show that LPS-mediated induction of TNF-α was suppressed by sodium butyrate. The discrepancy may be due to the difference in the cell type or the concentration of the sodium butyrate used. Sodium butyrate at higher concentration did inhibit the LPS-mediated induction of TNF-α in MEFs. Interestingly, caspase-11 induction following IFN-γ treatment was barely suppressed by sodium butyrate (Fig. 1C). Since it is well established that IFN-γ and LPS convey the signals via distinct pathways [31], these results imply that the suppression of caspase-11 induction by HDAC inhibitors was possibly mediated by modification of non-histone proteins.

Sodium butyrate inhibited the activation of JNK and p38 MAPK

To elucidate the mechanism of the suppression of caspase-11 induction by HDAC inhibitors, we then examined whether the HDAC inhibitors interfered with the upstream signaling events for the induction of caspase-11. Our results showing LPS-mediated caspase-11 induction was suppressed fairly efficiently by sodium butyrate (Fig. 1A) while IFN-γ-mediated caspase-11 was barely suppressed by the HDAC inhibitor imply that the effect of sodium butyrate on caspase-11 induction results mainly from changes in the upstream cytosolic signaling event rather than chromatin remodeling. Previously, it has been shown that caspase-11 induction is mediated by proinflammatory signaling involving the activation of p38 MAPK [27,34] and NF-κB [26,28]. In accordance with the previous report [27,32], inhibition of p38 MAPK with its pharmacological inhibitors such as SB202190 and SB203580 (30 μM) resulted in the suppression of caspase-11 induction as shown in Fig. 2A. In addition, a JNK inhibitor SP600125 (20 μM) suppressed the caspase-11 induction (Fig. 2A), suggesting that JNK as well as p38 MAPK plays a role to induce caspase-11 expression. To examine whether the HDAC inhibitor blocks the activation of these MAPKs and thereby suppresses the induction of caspase-11, sodium butyrate-pretreated MEFs were stimulated with LPS (100 ng/ml), and then the activation of p38 MAPK and JNK was examined by detecting the phosphorylated forms of these kinases at indicated times. As shown in Fig. 2B and C, sodium butyrate inhibited the phosphorylation of p38 MAPK and JNK p54. These results suggest that the HDAC inhibitor can block the cytosolic signaling event that leads to the induction of caspase-11. As to the mechanism of HDAC inhibitor suppressing the expression of proinflammatory genes, there have been seemingly conflicting observations: in certain cases HDAC inhibitors affected the upstream signaling events in the cytoplasm [8,9,13,33] but in other cases the inhibitors affected only the recruitment of NF-κB to a specific promoter but not the cytoplasmic events like activation of stress kinases or NF-κB translocation [7,34]. Again this discrepancy may result from the differences in the cell types and the nature of stimuli. However, our results clearly indicate that sodium butyrate can affect the activation of stress kinases involved in caspase-11 induction following LPS stimulation in MEFs.

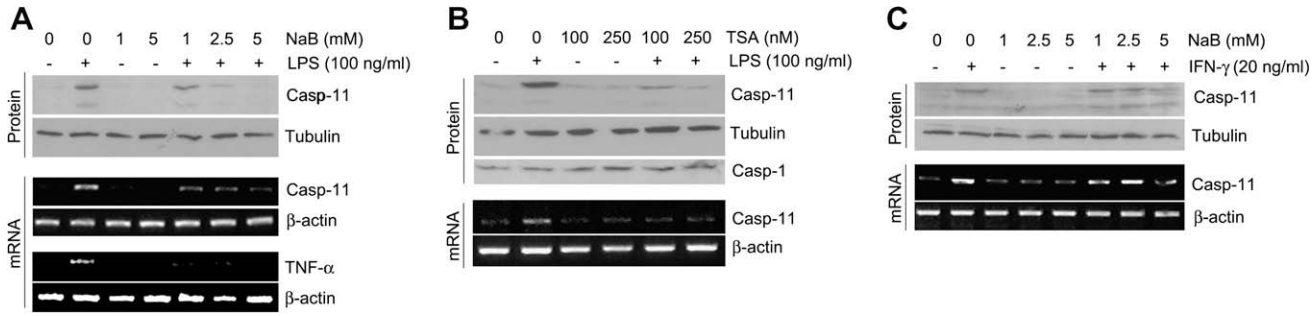

Fig. 1. HDAC inhibitors sodium butyrate and TSA suppressed the induction of caspase-11 in MEFs. (A) MEFs were 1 h pretreated with sodium butyrate (NaB; 1, 2.5, 5 mM) and stimulated with LPS (100 ng/ml). Then the expression of caspase-11 was examined by immunoblot (6 h LPS incubation) or RT-PCR (2 h incubation) analysis. Tubulin and β-actin served as internal controls in the immunoblot and RT-PCR, respectively. LPS-mediated induction of TNF-α was also inhibited by sodium butyrate pretreatment (bottom panels). (B) MEFs were 1 h pretreated with TSA (100 and 250 nM), stimulated with LPS (100 ng/ml), and then the expression of caspase-11 was examined by immunoblot after 6 h or RT-PCR after 2 h incubation with LPS. Protein level of caspase-1 was examined for comparison. (C) MEFs were 1 h pretreated with sodium butyrate (NaB; 1, 2.5, 5 mM), stimulated with IFN-γ (20 ng/ml) and then the expression level of caspase-11 was examined by immunoblot (6 h incubation with IFN-γ) or RT-PCR (2 h incubation with IFN-γ) analysis. Consistent results were obtained in at lease four independent experiments.

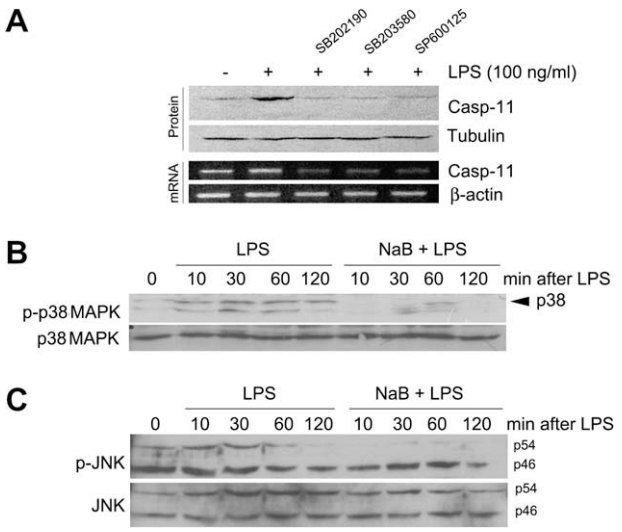

Fig. 2. Sodium butyrate inhibited LPS-induced activation of p38 MAPK and JNK. (A) To examine whether p38 MAPK or JNK is required for the induction of caspase-11, MEFs were pretreated with inhibitors of p38 MAPK (SB202190 and SB203580 at 30 μM) or JNK (SP600125 at 20 μM) for 30 min and stimulated with LPS (100 ng/ml). Then the expression of caspase-11 was examined by immunoblot analysis after 6 h or RT-PCR after 2 h incubation with LPS. (B,C) MEFs were 1 h pretreated with sodium butyrate (NaB; 2.5 mM), stimulated with LPS (100 ng/ml) for the indicated times and the activation of p38 MAPK (B) or JNK (C) was monitored by immunoblot using phospho-specific antibodies against each kinase. The level of total p38 MAPK or JNK served as control. Similar results were obtained in three independent experiments.

Sodium butyrate inhibited the degradation of IκBα and the phosphorylation of NF-κB p65

Since we observed the inhibition of p38 MAPK and JNK activation, we next examined whether the HDAC inhibitor affected NF-κB pathway. The NF-κB is present in the cytoplasm as an inactive form complexed with IκBα. Upon stimulation, IκBα is phosphorylated by IκBα kinase (IKK), ubiquitinated, and then degraded by 26 S proteasome, thereby facilitating NF-κB translocation into the nucleus [35]. MEFs were pretreated with sodium butyrate (2.5 mM) for 1 h, stimulated with LPS (100 ng/ml) and then the level of total IκBα (Fig. 3A) was examined by immunoblot. As shown in Fig. 3A, LPS induced the degradation of IκBα but the pretreatment of sodium butyrate suppressed the IκBα degradation. To examine whether the stabilization of IκB resulted from inhibition of IκBα phosphorylation, changes in the phosphorylation level with or without sodium butyrate pretreatment were monitored following LPS stimulation using antibodies specific for the phosphorylated IκBα. As shown in Fig. 3A, LPS stimulation induced the phosphorylation of IκBα, which was inhibited by sodium butyrate pretreatment. In accordance with these results, there have been studies reporting that sodium butyrate stabilizes IκB [9,32] and another HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) inhibits IKK activation and thus blocks ubquitination of IκBα in KBM-5 cells [8]. Since the stabilization of IκBα will hinder the phosphorylation of NF-κB [35], we then examined whether the HDAC inhibitor indeed suppressed the NF-κB phosphorylation. As shown in Fig. 3B, pretreatment of the MEFs with sodium butyrate suppressed the LPS-induced phosphorylation of NF-κB.

Sodium butyrate inhibited the nuclear translocation of NF-κB p65

Then we examined whether the HDAC inhibitor suppressed the translocation of NF-κB into the nucleus. MEFs were stimulated with LPS (100 ng/ml) with or without pretreatment of sodium butyrate (5 mM) and the localization of NF-κB was examined by immunocytochemistry. As shown in Fig. 4A, LPS induced the translocation of NF-κB into the nucleus but the pretreatment of sodium butyrate suppressed this translocation in many cells. The quantification of the NF-κB translocation shown in Fig. 4B indicates that sodium butyrate significantly suppressed the LPS-mediated nuclear translocation of NF-κB. However, we did not observe complete inhibition of the NF-κB translocation even when 5 mM sodium butyrate was used. The remaining portion of NF-κB translocation which was not inhibited by the sodium butyrate at the given concentration may reflect merely a concentration problem or a result of divergent LPS signaling. There have been reports suggesting that the HDAC inhibitor affected only the recruitment of NF-κB to specific promoters inside the nucleus but not the cytosolic signaling in mesangial cells stimulated with IL-1β or dendritic cells stimulated with LPS [7,34]. Thus, it is also possible that NF-κB that escaped the inhibition in the cytoplasmic signaling by sodium butyrate translocated into the nucleus but its recruitment to the caspase-11 promoter was hindered. However, many studies suggest that HDAC inhibitor can interfere with the cytosolic signaling events, specifically NF-κB translocation, for the proinflammatory gene induction [8,9,13,24]. A direct target of HDAC inhibitors in the cytoplasm during its anti-inflammatory action remains to be identified.

Overall, the present study showed that HDAC inhibitors suppressed the LPS-induced expression of caspase-11, which was mediated by inhibition of p38 MAPK and JNK activation and the nuclear translocation of NF-κB. Since caspase-11 is an inducible proinflammatory caspase that can promote maturation of several

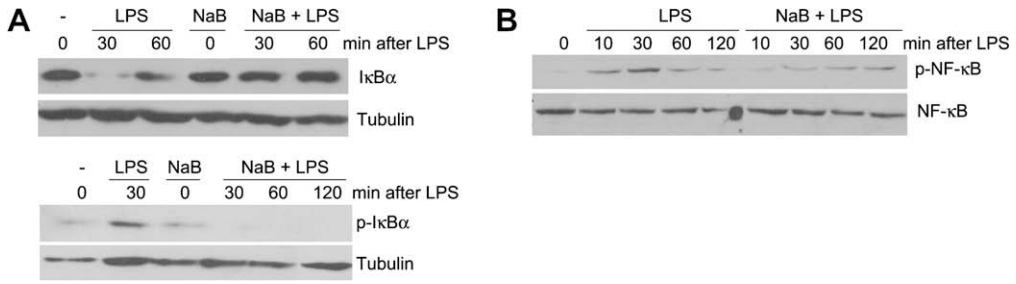

Fig. 3. Sodium butyrate inhibited the degradation of IκBα and the phosphorylation of NF-κB p65. (A) MEFs were 1 h preincubated with sodium butyrate (NaB; 2.5 mM), stimulated with LPS (100 ng/ml) and then the levels of total IκBα (top panels) and the phosphorylated forms (bottom panels) were examined by immunoblot at the indicated times after the LPS treatment. Tubulin served as a loading control. (B) Changes in the phosphorylation level of NF-κB were examined as in A using phospho-specific NF-κB and total NF-κB antibodies. Similar results were obtained in three independent experiments.

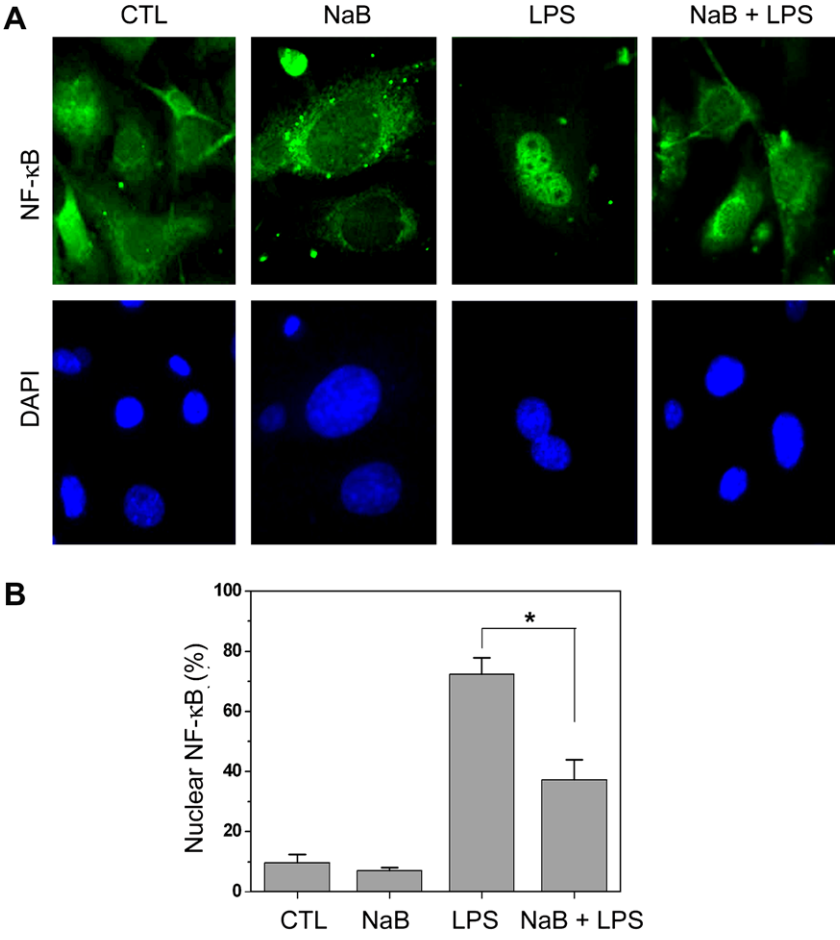

Fig. 4. Sodium butyrate inhibited the LPS-induced nuclear translocation of NF-κB. (A) MEFs were stimulated with LPS (100 ng/ml) following sodium butyrate (NaB; 5 mM) pretreatment for 1 h. After 1 h stimulation with LPS, the cells were processed for immunocytochemistry using anti-NF-κB antibodies. Quantification of the number of cells with nuclear NF-κB over the number of total cells is shown in (B) Over thousand cells (15 fields) were counted for each treatment group from the two independent experiments ($^{*}p < 0.05$, Student's *t*-test).

inflammatory cytokines, suppression of its induction will turn out to be very effective when anti-inflammation is required. We showed that HDAC inhibitors that have been known to suppress the induction of proinflammatory cytokines also suppress caspase-11 induction. In other words, the inhibitors of HDAC can suppress both synthesis and maturation of proinflammatory cytokines. Interestingly, Leoni et al. [6] observed a HDAC inhibitor SAHA reduced the LPS-induced release of TNF-α, IFN-γ, IL-12, and IL-1β in human peripheral blood mononuclear cells but the level of IL-1β mRNA or pro-IL-1β protein was unaffected. This discrepancy in SAHA's effect on released IL-1β and pro-IL-1β can be explained by our observation that HDAC inhibitors suppressed caspase-11 induction. If SAHA suppressed the induction of caspase-5, a human ortholog of caspase-11, in the peripheral blood mononuclear cells, the level of released IL-1β could be reduced even though SAHA did not suppress the induction of IL-β mRNA. Despite the conflicting observations on the mechanism of anti-inflammatory action of HDAC inhibitors, ample evidence including our results suggests that HDAC inhibitors will be of great value in treating many inflammatory diseases.

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