Enzyme Activation by Autocrine IL-10

Lipopolysaccharide-Induced IL-1β-Converting Enzyme Activation by Autocrine IL-10

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*Abstract*

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Janus Kinase 3 Down-Regulates Lipopolysaccharide-Induced IL-1β-Converting Enzyme Activation by Autocrine IL-10

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ProIL-1β processing by IL-1β-converting enzyme (ICE) and the subsequent release of mature IL-1β are highly regulated events in the monocyte/macrophage response to pathogens. This process occurs in a controlled way through the activation of the constitutively expressed 45-kDa ICE precursor (proICE). To characterize the signaling pathways involved in ICE regulation in human monocytes/macrophages, we analyzed ICE activation in the presence of specific inhibitors of classic signaling pathways. Although LPS-induced ICE activity was not significantly affected by interruption of extracellular signal-regulated kinase, p38 kinase, or phosphoinositol 3-kinase, Janus kinase 3 (JAK3) inhibition produced a significant dose-dependent enhancement of LPS-induced ICE activity. Support for the inhibitory role of JAK3 was shown by the fact that IL-4 (which uses JAK1 and JAK3 signaling) suppressed LPS-induced ICE activity and by the finding that JAK3 knockout macrophages have increased LPS-induced ICE activity. To understand how JAK3 down-regulates LPS-induced ICE activity in monocytes, we hypothesized that JAK3 signaling enhances IL-10 production. In support of this model we show that LPS-induced IL-10 expression was synchronous with ICE activation, IL-4 induced the release of IL-10, exogenous IL-10 suppressed LPS-induced ICE activity, a neutralizing IL-10 antibody (Ab) suppressed LPS-induced ICE activity and by the finding that JAK3 knockout macrophages displayed significantly reduced LPS-induced IL-10 production. These findings support a model in which JAK3 signaling enhances IL-10 production leading to down-regulation of ICE activation and suppression of IL-1β processing and release. The Journal of Immunology, 2004, 172: 4948–4955.

Interleukin-1β is a proinflammatory cytokine produced by blood monocytes and tissue macrophages that functions in innate host defense to induce inflammation. IL-1β is synthesized as an inactive precursor that requires a unique cysteine protease, IL-1β-converting enzyme (ICE,3 caspase-1) to generate a biologically active mature form (17 kDa) from proIL-1β (31 kDa) (reviewed in Ref. 1). As an innate immune mediator, IL-1β exerts clinically evident dual effects dependent on the level of production of its biologically active form. In moderate concentrations, IL-1β activates the NF-κB signaling pathway to express genes, including cytokines and chemokines, to alert other cells to danger as part of the protective immune response (reviewed in Ref. 2). However, overproduction of IL-1β can produce the features of septic shock, including hypotension, capillary leak, and acute respiratory distress syndrome (3–5). Conversely, underproduction of IL-1β can predispose to overwhelming infection and death (6, 7). Therefore, controlling the production of functional IL-1β is critical to proper functioning of an innate immune system. Improved understanding of this regulation is important to our ability to modify inflammation, host defense, and tissue injury.

In monocytes and macrophages, ICE activity seems to be tightly regulated to control excessive maturation of the proinflammatory cytokines IL-1β and IL-18 (8–11). Inactive proICE (p45; 45 kDa), containing an N-terminal caspase recruitment domain (CARD) (12), is induced by stimulants such as bacterial components, including LPS or other stimulatory cytokines (13, 14). Activation of proICE involves cleavages at four different aspartic acid residues to release CARD and yield p20 and p10 pieces that rearrange to form a functional tetramer, (p20/p10)2 (15–17). Each tetramer contains two active sites, which include the pentameric amino acid sequence (QACRG) of p20 and other components of p10 (15).

In the past decade, extensive research has provided a better understanding of how ICE is activated upon stimulation of monocytes/macrophages. Important advances include recognition of the critical involvement of a tyrosine kinase (18), identification of related CARD-containing proteins (reviewed in Refs. 19 and 20), and detection of a multimeric inflammatory complex made of ICE, caspase-5, apoptosis-associated speck-like protein, and the pyrin homologue NACHT-, LRR-, and PYD-containing protein-1 (21, 22). However, the details of ICE activation remain incomplete.

In this report, our data demonstrate the previously unrecognized role of Janus kinase 3 (JAK3) in the regulation of ICE activity. JAK3 is one of four known JAKs and is a nonreceptor tyrosine kinase functionally associated with cytokine receptors that share the common γ-chain (γc) of IL-2 family cytokine (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) receptors (reviewed in Refs. 23–25) (26). JAK3 mutations are not clinically distinguishable from the γc mutation, as both produce SCID (reviewed in Refs. 27 and 28) (29, 30). JAK3−/− mice grow normally in a pathogen-free environment. However, JAK3−/− mice show severe defects in lymphopoiesis and in negative selection of lymphocytes, indicating that JAK3 plays a key role in lymphoid development (31–33). JAK3 is predominantly expressed in cells of hematopoietic origin (reviewed...
in Refs. 23, 24, and 27). JAK3 is expressed at low, but detectable, levels in monocytes and is induced by LPS and IFN-γ (34).

We report in this study that a JAK3 signaling pathway negatively regulates LPS-induced ICE activation. One mechanism of this pathway is the inhibitory autocrine action of IL-10, which is induced by LPS through JAK3 signaling in LPS-stimulated monocytes/macrophages.

**Materials and Methods**

**Reagents**

Human recombinant cytokines (IL-1, IL-4, and IL-10) were purchased from R&D Systems (Minneapolis, MN). Caspase-1 Abs (G273 and R105) were gifts from Dr. D. Miller (Merck Research Laboratories, Rahway, NJ). Ac-YVAD-CHO, Ac-DEVAD-CHO, AG126, JANEX-1 (WHI-P131), SB202190, U0126, PP2, and wortmannin were obtained from Calbiochem (La Jolla, CA). Ac-WEHD-AMC and Ac-DEVAD-AMC were purchased from Calbiochem or Alexis Biochemicals (San Diego, CA). Bacterial LPS, *Escherichia coli* strain 0127:B8, Westphal preparation, was obtained from Difco (Detroit, MI). RPMI 1640 and PBS were purchased from BioWhitaker (Walkersville, MD), and FBS was obtained from HyClone (Logan, UT). All other reagents were obtained from Sigma-Aldrich (St. Louis, MO) unless otherwise specified.

**Isolation of human peripheral blood monocytes and cell culture**

Human peripheral blood monocytes were isolated from the heparinized blood of normal donors or buffy coats. First, PBMC were isolated by using Histopaque-1077 density gradient. Then monocytes were further purified with a system of MACS CD14 Microbeads (Miltenyi Biotec, Auburn, CA) for CD14+ monocytes. This method yields >95% pure monocytes. Isolated monocytes were cultured in a 5-ml polystyrene tube at 106 cells/ml in RPMI 1640 supplemented with 10% FBS at 37°C in humidified incubator, and all data from the assays were converted to 1 x 106 cells/ml. Typically LPS (1 μg/ml) were used to stimulate fresh monocytes along with other reagents (inhibitors or cytokines) as indicated.

**Preparation of cell lysates and Western blot**

After monocytes were treated, the culture media and cell pellets were collected by centrifugation at 800 x g for 10 min at 4°C. The cell pellets were washed with cold PBS three times. Cells were lysed in a cold lysis buffer (50 mM Tris-Cl (pH 8.0), 150 mM NaCl, 2 mM EDTA, and 1% Nonidet P-40) containing 10 μg/ml aprotinin, 1 μM bestatin hydrochloride, 1 μM pepstatin A, and 1 mM AEBSF on ice for 20 min at 4°C. The cell debris and nuclei were removed by centrifugation at 14,000 x g for 10 min at 4°C. The protein concentrations of the cell extracts were determined using a Bradford protein assay reagent (Bio-Rad, Hercules, CA) to load equal amounts of protein on a gel. The proteins were resolved by SDS-PAGE and transferred to a nitrocellulose membrane. Nonspecific amounts of proteins on a gel. The proteins were resolved by SDS-PAGE and were detected using a Cytofluor 4000 fluorometer (Perceptive, Framingham, MA) with filters of 360 nm excitation and 460 nm emission for 2 h at room temperature. The linear change of the fluorescence of hydrolyzed free AMC per time and the protein concentrations of the assayed samples were used for calculating a unit activity with a conversion factor obtained from the assay for constructing an AMC standard curve. The rate of ICE activity change was calculated by determining the difference in ICE activity between consecutive time points divided by the time elapsed. In a case of caspase-3 activity assay, Ac-DEVAD-AMC (35, 36) was used as a fluorogenic substrate.

**ICE ELISA**

A modified version of a sandwich ELISA (37) was constructed to detect ICE. Briefly, 96-well Immunolon IV plates (Dynatech, McLean, VA) were coated with protein G-purified G273, a goat polyclonal Ab generated against p20 and p10 ICE forms (also recognizes p45 forms). R105, a goat polyclonal Ab generated against p20 and p10 ICE forms (also recognizes p45 forms), was used as a sandwich Ab. The R105 was detected with a peroxidase-conjugated goat anti-rabbit Ab (Bio-Rad) and the TMB Microwell Peroxidase Substrate System (Kirkegaard & Perry, Gaithersburg, MD). Color development was stopped with 1 N H2SO4, and the resulting absorbance was read at 490 nm on an MR600 ELISA plate reader (Dynatech, Chantilly, VA).

**Human cytokine measurement**

Sandwich ELISAs were developed in our laboratory to detect pro- and mature IL-1β as previously described (38). The coating Ab has been modified since the previous description. Briefly, mouse monoclonal anti-human IL-1β Ab (clone 8156; R&D Systems) was used as the coating Ab, and rabbit polyclonal anti-human proIL-1β-specific peptide Ab generated against aa 3–21 was used to sandwich the Ag for the proIL-1β-specific ELISA. HRP-conjugated goat anti-rabbit Ab was used as a developing Ab. The mature IL-1β ELISA used the mAb clone 8156 and rabbit polyclonal mature IL-1β Ab (raised against entire 17-kDa mature IL-1β) as coating and sandwich Abs, respectively. Human IL-10 was measured using the Immulite automated chemiluminometer system (Diagnostic Products, Los Angeles, CA).

**Neutralization of LPS-induced IL-10**

After fresh monocytes were treated with human IgG (240 μg/ml) cells for 1 h to block nonspecific FcRs, monocytes were stimulated with LPS (1 μg/ml) in the presence of mouse IgG2b anti-human IL-10 mAb (clone 23738; MAB217; R&D Systems) or mouse IgG2b control mAb (clone 20116; MAB004; R&D Systems) for 7 h. Supernatants of the culture were subjected to ELISA for quantitating released mIL-1β. Cell pellets were subjected to measuring ICE activity using Ac-WEHD-AMC.

**Murine peritoneal macrophages**

JAK3 knockout (KO; 129S4-Jak3<sup>−/−</sup>) and control (C57Bl/6J) mice were purchased from The Jackson Laboratory (Bar Harbor, ME). To increase the numbers of peritoneal macrophages, wild-type (WT) and KO mice were injected with sterile thioglycollate 7 days before the experiments. Peritoneal macrophages of 11-wk-old mice were obtained from peritoneal lavage with saline solution. After washing with cold RPMI 1640, isolated macrophages were resuspended in RPMI 1640 containing 10% FBS plus a mixture of antibiotics (penicillin and streptomycin; Life Technologies, Gaithersburg, MD) at 1 x 10<sup>6</sup> cells/ml in a 5-ml polystyrene tube and treated with 1 μg/ml LPS or 1 μg/ml LPS plus 5 mM ATP at 37°C in humidified incubator for the indicated period.

**Murine cytokine measurement**

Cellular and released mouse IL-1β were measured with a sandwich ELISA system using rat monoclonal anti-mouse IL-1β Ab (clone 30311; MAB401; R&D Systems) and goat biotinylated anti-mouse IL-1β Ab (BAF401; R&D Systems) as coating and sandwich Abs, respectively. Streptavidin-conjugated HRP (Amersham Pharmacia Biotech) and the TMB Microwell Peroxidase Substrate System (Kirkegaard & Perry) was used for detection. Western blotting of IL-1β was conducted with goat anti-mouse IL-1β Ab (AF-401-NA; R&D Systems) and rabbit anti-goat Ab (Bio-Rad) as primary and secondary Abs, respectively. Released mouse IL-10 was measured using a mouse IL-10 ELISA kit (eBioscience, San Diego, CA).

**Statistical analysis**

Data are presented as the mean ± SD from at least three independent experiments. Simple comparisons were performed by Student’s t test, with p < 0.05 considered to represent statistical significance. In cases involving multiple comparisons, the Bonferroni correction was used (39).
JAK3 DOWN-REGULATES LPS-INDUCED ICE ACTIVITY VIA IL-10

Results

JAK3 inhibitor modulates ICE activation

In efforts to identify a signaling molecule(s) or upstream enzyme(s) that modulates ICE activation in monocytes, we tested several specific kinase inhibitors (Fig. 1). Compared with the control (DMSO), AG126 decreased ICE activity by as much as 80%. Wortmannin (a phosphoinositol 3-kinase inhibitor) minimally decreased ICE activity, whereas PP2 (an Src kinase inhibitor), SE202190 (p38 mitogen-activated protein kinase inhibitor), and Wortmannin minimally decreased ICE activity, whereas PP2 (an Src kinase inhibitor), SE202190 (p38 mitogen-activated protein kinase inhibitor), and Wortmannin (a phosphoinositol 3-kinase inhibitor) did not affect ICE activity. However, interestingly, JANEX-1 (WHI-P131; a specific JAK3 kinase inhibitor) (40) dramatically increased ICE activity (Fig. 1). This unexpected observation led us to hypothesize that JAK3 signaling is involved in the down-regulation of LPS-induced ICE activation in monocytes.

The effect of JANEX-1 on LPS-induced ICE activity was dose dependent. Treatment with higher doses of JANEX-1 resulted in higher ICE activity in LPS-stimulated monocytes (Fig. 2). It was previously reported that JANEX-1 concentrations <350 μM (<100 μg/ml) do not inhibit JAK1 or JAK2 activities (40, 41); therefore, the observed effect is probably due to specific inhibition of the JAK3 pathway.

IL-4 suppresses ICE activation and JAK3 inhibition blocks the suppression

IL-4, an IL-2 family cytokine, transduces its signals via JAK1 and JAK3. Fresh monocytes were treated with LPS (1 μg/ml) in the presence or the absence of IL-4 (20 ng/ml) and/or JANEX-1 (50 μg/ml) for 5 h and assayed for ICE activity by cleavage of Ac-WEHD-AMC (Fig. 3). LPS alone induced ICE activation, and the addition of JANEX-1 further increased LPS-induced ICE activity. As expected, treatment with IL-4 reduced LPS-induced ICE activity by 30–60%, supporting the hypothesis that JAK signaling is involved in the down-regulation of ICE activation. Furthermore, the inhibitory effect of IL-4 on LPS-induced ICE activity was blocked with the JAK3 inhibitor, demonstrating that the IL-4 effect on the down-regulation of LPS-induced ICE activation requires JAK3.

JAK3−/− mice show enhanced LPS-induced inflammation

To further demonstrate that JAK3 is involved in suppressing ICE activity, JAK3−/− mice were compared with WT mice for LPS-induced ICE activity in peritoneal macrophages. Thioglycolate-induced peritoneal macrophages from JAK3−/− and WT mice were harvested and stimulated with LPS (1 μg/ml) or LPS, followed by ATP (5 mM) for the final 30 min, as ATP has been shown to increase LPS-induced ICE activity in monocytes (18). Supernatants were analyzed for released mature IL-1β as an indirect assessment of ICE activity, as processing of proIL-1β requires ICE. The levels of released mature IL-1β from LPS-stimulated or LPS- plus ATP-stimulated JAK3−/− macrophages were approximately double those from WT macrophages, as quantified by ELISA (Fig. 4A) and confirmed by Western blot (Fig. 4B), suggesting that higher ICE activity was induced in the LPS-stimulated JAK3−/− macrophages. This difference in release was not due to higher proIL-1β synthesis in the JAK3−/− macrophages, as quantified by ELISA (Fig. 4C) and confirmed by Western blot (Fig. 4D). This demonstration provides ex vivo evidence that JAK3 is involved in suppressing LPS-induced or LPS- plus ATP-stimulated ICE activity.

JAK3 pathway produces IL-10 in monocytes/macrophages

To better understand how JAK3 reduced LPS-induced ICE activity, we investigated the kinetic effects of LPS on the patterns of
LPS-inducible cytokine production. In LPS-stimulated monocytes, we observed that the peak rate of ICE activation and mature IL-1β release occurred 5 h after LPS addition (Fig. 5, A and B, respectively). Of note, however, IL-4 was not detected in monocyte supernatants. Nevertheless, the related inhibitory cytokine IL-10 was detectable. IL-10 was first detected at 5 h and rapidly increased after 5 h (Fig. 5C), although proinflammatory cytokines, TNF-α, IL-1β, IL-6, and IL-8, were detected as early as 2 h in monocyte medium (data not shown). The period of rapid increase in IL-10 overlapped with the deactivation period of ICE.

To determine whether the JAK3 pathway might induce the suppressive cytokine IL-10, we next asked whether a JAK3 stimulant, such as IL-4, might induce IL-10. IL-4 was added to LPS-treated monocytes. Early addition of IL-4 to LPS-treated monocytes suppressed the production of inflammatory IL-1β (Fig. 6A). In contrast, early addition of IL-4 to LPS-treated monocytes increased production of anti-inflammatory IL-10 (Fig. 6B). To confirm that JAK3 signaling plays a role in IL-10 production, we next measured the level of IL-10 production after treating LPS-stimulated monocytes with the JAK3 inhibitor. Fig. 7 demonstrates that JAK3 inhibition inhibited IL-10 production in LPS-stimulated monocytes.

As an additional approach, we compared LPS-induced IL-10 production in WT and JAK3−/− macrophages. In this study macrophages were stimulated with LPS (1 μg/ml), and the supernatants were collected 7 and 16 h poststimulation and analyzed by ELISA. The results indicated that IL-10 production was significantly lower in JAK3−/− macrophages (Fig. 8), suggesting that JAK3 is necessary for efficient production of IL-10.

**LPS-induced IL-10 down-regulates ICE activation**

Finally, to determine the causal effect of IL-10 in modulating ICE activity, we tested the ability of exogenous IL-10 and of IL-10 blockade to modulate LPS-induced monocyte ICE activation. After monocytes were pretreated with excess human IgG to block nonspecific binding sites of FcRs, the monocytes were treated with LPS in the presence of IL-10 or IL-10 Ab. The effect on ICE activity is summarized in the Table I. Exogenous IL-10 (10 ng/ml) indeed decreased LPS-induced ICE activity (40–60%), and the suppressive effect was dose dependent (data not shown). Although a control mAb did not significantly affect the LPS-induced ICE activity (90–110%), a neutralizing IL-10 mAb augmented LPS-induced ICE activity (140–150%). The effect on IL-1β release paralleled the effect on ICE (Table I). These observations support the concept that LPS-induced IL-10 negatively regulates LPS-induced ICE activation in monocytes.

**Discussion**

Our findings document for the first time that JAK3 signaling is involved in the regulation of ICE activation. The JAK3 pathway functions to down-regulate ICE, as evidenced by the following
findings. First, the inhibition of JAK3 by the JAK3-specific inhibitor (JANEX-1) increased LPS-induced ICE activity in a dose-dependent manner. Second, treatment with exogenous IL-4 (which signals via JAK1 and JAK3) suppressed LPS-induced ICE activity. Third, the suppressive effect of IL-4 was blocked by the addition of JANEX-1, confirming the participation of JAK3. Finally, JAK3 KO macrophages demonstrated enhanced mature IL-1β release upon LPS stimulation, indicative of increased LPS-induced ICE activity.

Having made the link between JAK3 and ICE activities, we next turned to understanding how this may occur. To investigate this, we evaluated the role of IL-10 in this pathway. We showed that 1) IL-4, which works through a JAK3 mechanism, induced IL-10 production by monocytes when copresented with LPS; 2) the time course of LPS-induced IL-10 production from monocytes corresponded with the decrease in ICE activation; 3) JAK3 KO macrophages showed significantly reduced IL-10 release compared with its WT macrophages; 4) the exogenous addition of IL-10 to monocytes suppressed their ICE activation; and 5) blockade of autocrine IL-10 function with an Ab to IL-10 significantly enhanced ICE activation. Taken together, these observations indicate that JAK3 signaling suppresses LPS-induced ICE activation at least in part by promoting IL-10 production.

As mentioned, we could not detect significant production of IL-4 in our purified monocyte preparations, but subsequent experiments may explain how JAK3 functions in our LPS model. IL-4 binds to a complex receptor system composed of one IL-4R α-chain (which associates with JAK1) and the IL-2R γc (which associates with JAK3) (reviewed in Refs. 23, 24, and 27). The γc is necessary for IL-4 regulation of LPS-induced IL-10 production.
in monocytes/macrophages (42). It appears that a similar pathway is used in LPS-stimulated monocytes, as we showed that JANEX-1, a JAK3-specific inhibitor, suppressed IL-10 production in a dose-dependent fashion. Thus, LPS stimulation induces IL-10 in a JAK3-dependent fashion.

In summary, our results suggest that ICE activity may be controlled by suppressive cytokines. Because a JAK3 inhibitor promoted ICE activity, we initially focused on IL-4 as it signals through JAK3. IL-4 inhibited ICE activity in a JAK3-dependent fashion. However, IL-4 was not induced in our monocyte model. In contrast, IL-10, another classic suppressive cytokine, but one that does not signal through JAK3, was induced by LPS. In this regard, we were able to demonstrate that blockade of IL-10 enhanced ICE activation, and induction of IL-10 suppressed ICE activation. Thus, one might conclude that IL-10 and JAK3 are parallel pathways, and both function to suppress ICE activity. Nevertheless, IL-4 induced IL-10 production via a JAK3-dependent pathway (Fig. 6), and importantly, LPS induced IL-10 via JAK3 (Figs. 7 and 8). Thus, we believe that the data presented in this study support the hypothesis that JAK3 activation is upstream of IL-10, providing a common pathway to down-regulate ICE activation.

The connections between JAK3 signaling and LPS-induced ICE activity or LPS-induced IL-10 are novel. However, the mechanism(s) by which IL-10 inhibits ICE activation remains to be elucidated. One potential explanation may be via the ability of IL-10 to influence the inflammasome. The inflammasome functions to activate ICE and requires a concerted action of several PYRIN- and CARD-containing proteins (21). Of note, in murine macrophages, both IL-10 and IL-4 induce pyrin (43). Pyrin interacts with a CARD of apoptosis-associated speck-like protein (44), which activates ICE (22), leading to inhibition of IL-1β processing in macrophages (43). In fact, ICE activation is enhanced in pyrin-mutant macrophages (43). These results support the possibility that pyrin is a downstream effector of IL-10. Interestingly, IL-10-induced pyrin expression is diminished in JAK3 KO macrophages (43). Taken in the context of our recent findings linking JAK3 to ICE activation, pyrin is a strong candidate to be the mediator of the JAK3 effect.

Another example to support a connection between LPS-induced ICE activity and the level of LPS-induced IL-10 is the difference between monocytes and macrophages in IL-1β processing and release. Monocytes are highly inducible to process and release IL-1β compared with macrophages, despite similar levels of total IL-1β production and proICE (37, 45). This observation is in line with our findings that LPS-induced ICE activity in macrophages is lower (37). In this context, it is remarkable that macrophages produce more IL-10 (~2.5-fold) upon LPS stimulation than monocytes (42). Thus, the previously recognized discrepancy between monocytes and macrophages for IL-1β processing and release may be explained by differences in LPS-induced IL-10 and, hence, differences in LPS-induced ICE activity.

Besides the induction of the inhibitory pyrin, other potential mechanisms by which IL-10 may be involved in suppressing LPS-induced ICE activation include 1) the induction of the suppressor of cytokine synthesis-3 through a STAT3-dependent pathway (46-
48); and 2) inhibition of NF-κB activity (49) by blocking NF-κB nuclear translocation via suppressing IKK activity or by blocking DNA binding of NF-κB already present in the nucleus (50).

Dysregulation of IL-1β processing and release is linked with severe clinical disease, such as sepsis, acute respiratory distress syndrome, rheumatoid arthritis, and overwhelming infection (3–7, 51). Also, IL-1α, another proinflammatory cytokine activated by ICE, is involved in numerous diseases, such as sepsis, myocardial suppression, collagen-induced arthritis, inflammatory bowel disease, and hepatic injury (reviewed in Ref. 52). In addition to providing resistance to endotoxic shock (53), the ICE KO state reduces symptoms related to endotoxic shock (53), the ICE KO state reduces symptoms related to acute dextran sodium sulfate-induced colitis in mice, providing evidence for an anti-inflammatory strategy for intestinal inflammation (54). Abnormal levels of IL-10 seem to be connected to pathological inflammation, collagen-induced arthritis, in patients with inflammatory bowel disease and psoriasis (reviewed in Ref. 48). Numerous studies of IL-10 have demonstrated that IL-10 can be used as a therapeutic tool in pathologic diseases.

Our present report not only provides mechanistic insight into the down-regulation of the inflammatory process via JAK3-mediated reduction of IL-1β activity, but may provide additional biological plausibility for the role of IL-10 therapy in the management of proinflammatory disease states.

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References


