Interleukin-4 and -13 Inhibit Tumor Necrosis Factor-α mRNA Translational Activation in Lipopolysaccharide-induced Mouse Macrophages*

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The production of tumor necrosis factor-α (TNF-α) by lipopolysaccharide (LPS)-stimulated macrophages can be markedly inhibited by the two closely related cytokines, interleukin (IL)-4 and IL-13. To investigate the molecular mechanism of this inhibition, we analyzed the effect of the two cytokines on TNF-α production and TNF-α mRNA accumulation in the mouse macrophage cell lines RAW 264.7 and J774 stimulated by LPS. Whereas LPS-induced TNF-α production is strongly suppressed by both cytokines, TNF-α mRNA accumulation is not significantly affected, indicating that IL-4 and IL-13 induce a translational repression of TNF-α mRNA. Transfection of reporter gene constructs containing different regions of the TNF-α gene revealed that the inhibitory action of IL-4 and IL-13 is mediated by the UA-rich sequence present in the TNF-α mRNA 3′-untranslated region.

Tumor necrosis factor-α (TNF-α) is a pleiotropic cytokine secreted by different cell types including macrophages, mastocytes, T and B lymphocytes, and natural killer cells in response to various stimuli (lipopolysaccharide [LPS], viruses, parasites, etc.) (1). A wide variety of cell types express TNF-α receptors, and the pleiotropism of TNF-α results from the complexity of the signal transduction pathways that are activated by its receptors. TNF-α is characterized by cytostatic and cytolytic effects on tumor cells of different origins (2), by antiviral properties (3), and by its important role in the activation of the immune system upon host invasion (4). TNF-α has also been identified as a major mediator of inflammatory processes, one of the most dramatic being Gram-negative septic shock (1). Indeed, upon exposure to LPS or other agents simulating host invasion, macrophages produce large amounts of TNF-α that are released in the circulatory system. High levels of circulating TNF-α trigger a state of shock and tissue injury that carries an extremely high mortality rate (1).

The expression of the TNF-α gene in mouse macrophages is regulated at the transcriptional (5, 6) and translational (1) levels. In resting macrophages, TNF-α synthesis is low because TNF-α gene transcription is weak and TNF-α mRNA translation is severely repressed. The translational repression is mediated by the UA-rich sequence present in the TNF-α mRNA 3′-untranslated region (1). Macrophage activation by LPS results in NF-κB-dependent activation of TNF-α gene transcription, derepression of TNF-α mRNA translation, and secretion of TNF-α protein. TNF-α production by macrophages can be down-regulated by various agents including cytokines like IL-4 and IL-13 (7, 12). IL-4 and IL-13 are closely related cytokines that are synthesized mainly by activated T lymphocytes (7, 8). Both cytokines share many biological activities including the activation of B cell proliferation, IgE switching, and inhibition of inflammatory cytokine production (9–11). TNF-α is one of the major inflammatory cytokines being repressed by IL-4 and IL-13. However, the molecular mechanism of this regulation has not been elucidated. In this study, we investigated the mechanism by which IL-4 and IL-13 down-regulate TNF-α production in LPS-stimulated mouse RAW 264.7 and J774 macrophages. We show that in these cell types, IL-4 and IL-13 inhibit LPS-induced TNF-α production mainly at the translational level. Furthermore, down-regulation of TNF-α mRNA translation by IL-4 and IL-13 is mediated by the UA-rich sequence present in its 3′-untranslated region.

MATERIALS AND METHODS

Reagents—LPS from Escherichia coli (strain 0.127:B8) was obtained from Sigma. [α-32P]UTP (800 Ci/mmol) and [3H]choloramphenicol (56 mCi/mmol) were purchased from Amersham Life Science, Inc. Murine recombinant IL-4 and TNF-α were purchased from Genzyme. Purified murine IL-13 was obtained from Sanofi Elf Biorecherches, Labège, France.

DNA Constructs—Both reporter constructs used in this study have been described elsewhere: CMV3-TNF in Ref. 13 and CMV3-TNFαA in Ref. 14, referred to as construct 3.

Cell Culture, Transfection, and Treatments—The murine macrophage cell lines RAW 264.7 and J774 were obtained from the American Type Culture Collection. The cells were maintained in Dulbecco’s modified Eagle’s medium containing 5% fetal bovine serum (FBS Mycolone Super Plus, Life Technologies, Inc.) and 1% penicillin/streptomycin. RAW 264.7 cells were cotransfected with each of the described constructs and pSV2Neo as described (15). Cells were first selected for 1 day with 0.3 mg/ml G418 sulfate, for 1 day with 0.6 mg/ml, and for 2 weeks with 1 mg/ml. The resistant clones were then pooled. The cells were stimulated simultaneously with LPS (10 ng/ml) and IL-4 (5 ng/ml) or IL-4 (5 ng/ml) or IL-13 (5 ng/ml) unless otherwise specified.

Measurement of TNF-α Production—TNF-α levels were measured in cell supernatants by sandwich enzyme-linked immunosorbent assay using a polyclonal rabbit anti-mouse TNF-α antibody for coating and the same biotinylated polyclonal antibody for detection (generously provided by Dr. W. Buurman, University of Limburg Maastricht, The Netherlands).
Translational Suppression of TNF-α mRNA by IL-4 and IL-13

Inhibition of LPS-induced TNF-α Production by IL-4 and IL-13 in RAW 264.7 and J774 Mouse Macrophages—RAW 264.7 mouse macrophages produce large amounts of TNF-α in response to LPS. Moreover, the transcriptional and post-transcriptional regulation of TNF-α biosynthesis by LPS is well characterized in this cell line. Therefore, RAW 264.7 cells provided an appropriate system to analyze the mechanism by which IL-4 and IL-13 suppress LPS-induced TNF-α production. We also analyzed the mechanism by which these cytokines down-regulate LPS-induced TNF-α production in J774 cells, which produce high levels of TNF-α upon LPS stimulation.

A recent study has shown that depending on the time of exposure to IL-4 or IL-13 relative to LPS stimulation, IL-4 and IL-13 have either inhibitory or stimulatory effects on LPS-induced TNF-α production in human peripheral blood mononuclear cells (18). When added to the cell culture 20 h or more before LPS stimulation, IL-4 and IL-13 prime LPS-induced TNF-α production, whereas when added simultaneously or a few hours before LPS stimulation, IL-4 and IL-13 exert a marked inhibitory effect on the production of this cytokine (18). Therefore, before analyzing the mechanism by which these cytokines inhibit LPS-induced TNF-α production, we verified that IL-4 and IL-13, when added to the cell culture at the same time as LPS, could inhibit TNF-α production in RAW 264.7 and J774 cells. We performed experiments in which increasing concentrations of each cytokine were added to RAW 264.7 or J774 cell cultures simultaneously with LPS. TNF-α production was assayed by enzyme-linked immunosorbent assay using a polyclonal anti-mouse TNF-α antibody to measure the total amount of TNF-α produced in response to the various treatments. As shown in Fig. 1, LPS-induced TNF-α production in RAW 264.7 cells was inhibited by both cytokines in a dose-dependent manner, reaching 72 and 63% inhibition at the highest doses of IL-4 and IL-13 tested, respectively (IL-4, 5 ng/ml; and IL-13, 5

**RESULTS**

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**FIG. 1.** Inhibition of LPS-induced TNF-α production by increasing doses of IL-4 (A) or IL-13 (B) in RAW 264.7 (solid bars) and J774 (striped bars) cells. Cells were plated at a density of 1.5 × 10⁶ cells/well in 24-well plates. When the cells were adherent, they were either untreated or treated with LPS (10 ng/ml) alone or in combination with IL-4 or IL-13 at the indicated concentrations. After 6 h of incubation, the cell culture media were harvested to measure TNF-α production. The induction of TNF-α production by LPS in the presence of either cytokine is expressed in percent, attributing 100% to the level of TNF-α produced by cells treated by LPS alone in comparison with the level of TNF-α produced by unstimulated cells. Results are the means ± S.E. from three separate experiments.

CAT Assay—CAT assays were performed as described (17), and quantification of CAT activity was performed with a Molecular Dynamics PhosphorImager.

Northern Blot Analysis—Northern blot analysis was performed as described (16) using 10 and 20 μg of total cytoplasmic RNA for TNF-α and CAT mRNA detection, respectively. Blots were hybridized with antisense riboprobes for TNF-α and CAT mRNAs (16, 17). For quantification, the blots were rehybridized with a glyceraldehyde-3-phosphate dehydrogenase antisense riboprobe. RNA quantification was achieved by normalizing the radioactive signal corresponding to TNF-α mRNA to that of glyceraldehyde-3-phosphate dehydrogenase in the same RNA sample.

**RESULTS**

**Inhibition of LPS-induced TNF-α Production by IL-4 and IL-13 in RAW 264.7 and J774 Mouse Macrophages**—RAW 264.7 mouse macrophages produce large amounts of TNF-α in response to LPS. Moreover, the transcriptional and post-transcriptional regulation of TNF-α biosynthesis by LPS is well characterized in this cell line. Therefore, RAW 264.7 cells provided an appropriate system to analyze the mechanism by which IL-4 and IL-13 suppress LPS-induced TNF-α production. We also analyzed the mechanism by which these cytokines down-regulate LPS-induced TNF-α production in J774 cells, which produce high levels of TNF-α upon LPS stimulation.

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IL-4 and IL-13 Inhibit LPS-induced TNF-α Production at the Translational Level—TNF-α production by LPS-stimulated mouse macrophages results from a combination of TNF-α gene transcriptional activation and TNF-α mRNA translational derepression. To determine at which level IL-4 and IL-13 inhibit LPS-induced TNF-α production, we analyzed LPS-induced TNF-α mRNA accumulation in the presence of either cytokine. Since TNF-α mRNA accumulation peaks 2 h after LPS addition to the cell culture (19), we studied the effect of IL-4 and IL-13 on the accumulation of the TNF-α mRNA at this time point. As shown in Fig. 3A, both IL-4 and IL-13 markedly reduced the accumulation of TNF-α mRNA by LPS alone (38-40% compared to the control, respectively). These results are in agreement with former studies showing that IL-4 and IL-13 inhibit the expression of the TNF-α gene (19).

IL-4 and IL-13 Inhibit LPS-induced TNF-α Production. In contrast to the inhibition of TNF-α mRNA accumulation, both IL-4 and IL-13 had no effect on TNF-α production. Indeed, former studies showed that in RAW 264.7 cells transfected with this construct, LPS stimulates the expression of the reporter gene by acting only at the translational level (13). In unstimulated RAW 264.7 cells, the presence of the CMV promoter led to the constitutive accumulation of CMV3-TNF mRNA as evaluated by Northern blotting, but this mRNA was poorly translated in CAT protein (Fig. 5A). Upon stimulation with LPS, translational derepression resulted in CAT protein accumulation without significant variation of the CMV3-TNF mRNA. Exposure of the CMV3-TNF-transfected cells to LPS in combination with IL-4 or IL-13 markedly reduced the accumulation of CAT activity (Fig. 5A) without affecting the level of CMV3-TNF mRNA. In contrast, IL-4 and IL-13 had no effect on the expression of the CMV3-TNF mRNA in RAW 264.7 cells (data not shown). These results indicate that IL-4 and IL-13 suppress the expression of the CMV3-TNF reporter gene at the translational level and require the presence of the UA-rich sequence to exert their inhibitory action on TNF-α mRNA translation.

DISCUSSION

It is now well established that in monocytes/macrophages, IL-4 and IL-13 mediate several similar functions, among which one of the major is the inhibition of proinflammatory cytokine production. Indeed, both IL-4 and IL-13 inhibit the production of several cytokines including IL-1α, IL-1β, IL-6, IL-12, macrophage inflammatory protein-α, granulocyte/macrophage colony-stimulating factor, granulocyte colony-stimulating factor, interferon-α, and TNF-α by monocytes/macrophages activated with LPS (7, 10, 12, 20). The inhibitory effect of IL-4 and IL-13...
on the production of TNF-α has been demonstrated in human peripheral blood monocytes (7, 10–12, 21, 22), human alveolar macrophages (23), murine bone marrow macrophages (11, 20) and murine peritoneal macrophages (24). The mechanism by which IL-4 and IL-13 inhibit LPS-induced TNF-α production in monocytes/macrophages is still controversial. For instance, several studies show that IL-4 and IL-13 decrease LPS-induced TNF-α mRNA accumulation in human peripheral blood mononuclear cells (7, 21, 22). However, one report describes that in mouse peritoneal macrophages, IL-4 does not modify TNF-α mRNA accumulation in response to LPS (24). The expression of the TNF-α gene in macrophages is regulated both at the transcriptional and post-transcriptional levels (1). In unstimulated mouse macrophages, TNF-α production is severely repressed both at the transcriptional and translational levels. Indeed, under these conditions, TNF-α gene transcription is poor, and TNF-α mRNA translation is blocked. This translational repression is mediated by the UA-rich sequence located in the 3′-untranslated region of TNF-α mRNA. Macrophage activation by LPS leads to a 50-fold increase in TNF-α gene transcription and a 200-fold increase in TNF-α mRNA translation, leading to an overall 10,000-fold increase in TNF-α biosynthesis (1). Translational regulation of TNF-α mRNA also plays an important role under other circumstances. Indeed, LPS tolerance, which is characterized by an impaired TNF-α production in response to a secondary LPS challenge, is mainly due to a defective translation of TNF-α mRNA (14). Furthermore, production of TNF-α in response to infection by several viruses (Sendai virus, Newcastle disease virus, vesicular stomatitis virus, vaccinia virus, and Mengo virus) results to a great extent from TNF-α mRNA translational activation (25).

In our study, we aimed at determining the mechanism by which IL-4 and IL-13 inhibit LPS-induced TNF-α production in the mouse macrophage cell line RAW 264.7, in which the regulation of TNF-α biosynthesis is well characterized. Furthermore, we also investigated this regulatory mechanism in another mouse macrophage cell line, J774, which also produces high levels of TNF-α in response to LPS. We first verified that IL-4 and IL-13 down-regulate TNF-α production in both cell types when added to the cell culture at the same time as LPS. We then demonstrated that under these conditions, both cytokines inhibit LPS-induced TNF-α production without significantly affecting TNF-α mRNA accumulation. Therefore, we conclude that IL-4 and IL-13 down-regulate TNF-α gene expression at the translational level. By analyzing the effect of IL-4 and IL-13 on the expression of CAT reporter DNA constructs with or without the TNF-α mRNA UA-rich sequence in RAW 264.7 cells, we show that both IL-4 and IL-13 exert their inhibitory action on mRNA translation through the intermediate of this UA-rich sequence. Recently, we have identified in RAW 264.7 cells a protein complex that binds the TNF-α mRNA UA-rich sequence upon stimulation with LPS (26). The LPS-induced binding of this complex to the UA-rich sequence requires tyrosine phosphorylation since it is blocked by the protein tyrosine phosphorylation inhibitor herbimycin A. The observation that IL-4 and IL-13 affect TNF-α mRNA translation suggests that IL-4 and IL-13 might interfere with the binding of this protein complex to the UA-rich sequence upon LPS stimulation. The mechanism by which this phenomenon might occur is still speculative. However, it is well known that stimulation of macrophages by LPS promotes tyrosine phosphorylation of various members of the serine/threonine mito-

![Fig. 5. IL-4 and IL-13 inhibit LPS-induced translation of a CAT reporter construct containing the full-length TNF-α 3′-untranslated region. A, CAT activity and Northern blot analysis of CAT mRNA accumulation in RAW 264.7 cells stably transfected with the CMV3-TNF construct after stimulation with LPS alone or in combination with IL-4 or IL-13; B, CAT activity and Northern blot analysis of CAT mRNA accumulation in RAW 264.7 cells stably transfected with the CMV3-TNFUA construct after treatment with LPS alone or in combination with IL-4 or IL-13. Cells were plated at a density of 10 × 10⁶ cells in 10-cm dishes. When the cells were adherent, they were either untreated or treated with LPS (10 ng/ml) alone or in combination with IL-4 (5 ng/ml) or IL-13 (5 ng/ml). After 3 h of incubation, the cells were harvested. 10⁶ cells were used for CAT production; 10⁶ cells were used to extract cytoplasmic RNA for Northern blot analysis. CAT production is expressed in percent, attributing 100% to the level of CAT activity produced by the cells treated with LPS alone. The results show one representative out of three independent experiments. A maximal 10% variation was observed in the level of CAT mRNA accumulation and in the degree of inhibition of CAT protein production by IL-4 and IL-13. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; AcCM, acetylated forms of chloramphenicol; CM, chloramphenicol.](Image)
gen-activated protein kinase family, including mitogen-activated protein kinases, mitogen-activated protein kinase-like p38, and its human homologs CSBP1 and CSBP2, resulting in an increase in their kinase activity (27–32). Interestingly, inhibitors of CSBP1 and CSBP2 kinase activity specifically impair LPS-induced TNF-α mRNA translation by preventing TNF-α mRNA recruitment into polysomes upon LPS stimulation (33). These observations indicate that p38 and CSBPs are the LPS-signaling intermediates that mediate TNF-α mRNA translational activation most probably by triggering the binding of the protein complex to the UA-rich sequence.

How do IL-4 and IL-13 down-regulate LPS-induced TNF-α mRNA translation? Both cytokines share a common receptor subunit, IL-4 receptor-a, which is essential for intracellular signaling (34). Upon IL-4 or IL-13 stimulation, IL-4 receptor-a becomes phosphorylated on tyrosine residues and recruits several signaling proteins including 4PS (also called IRS-2). 4PS, which also becomes phosphorylated on tyrosine residues, forms a signaling complex containing phosphatidylinositol 3-kinase, the adapter molecules GRB/Sos and Nck, and the tyrosine phosphatase PTP1D (also known as SH-PTP2 or Syp) (35, 36). So far, no downstream signals originating from GRB/Sos, Nck, and PTP1D have been observed upon IL-4/IL-13 stimulation, and the significance of their recruitment by 4PS remains unclear. We can speculate that upon IL-4 or IL-13 stimulation, the tyrosine phosphatase activity of PTP1D might down-regulate the kinase activity of p38 and CSBP1 and CSBP2 by controlling their phosphorylation status. Consequently, the LPS-induced binding of the protein complex to the UA-rich sequence and TNF-α mRNA translation would be inhibited.

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