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J Immunol 2003; 170:6202-6208; doi: 10.4049/jimmunol.170.12.6202
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Regulation of Chemokine mRNA Stability by Lipopolysaccharide and IL-10

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IL-10 has been reported to inhibit the expression of LPS-induced proinflammatory cytokines and chemokines by altering the rate of specific mRNA decay although the molecular target(s) for its action remain unknown. In the present study, using primary peritoneal exudate macrophages and a cell culture model in which a tetracycline-responsive promoter controls transcription of CXC ligand 1 (KC) mRNA, we demonstrate that LPS promotes a time-dependent increase in KC mRNA stability. Although IL-10 had no direct effect on mRNA decay, this treatment antagonized the stabilizing action of LPS. The mechanisms involved were further explored using a cell-free mRNA degradation system. A 5'-capped, polyadenylated in vitro transcript derived from the 3'-untranslated region of KC mRNA exhibited time-dependent decay in the presence of protein extracts prepared from untreated RAW264.7 macrophages. Extracts prepared from LPS-treated RAW264.7 cells had reduced decay activity and this change was antagonized if the cells were costimulated with IL-10. A substrate in which the AU-rich element motifs were mutated exhibited minimal decay that did not vary using extracts prepared from cells treated with LPS or LPS and IL-10. A nonadenylated RNA substrate was also degraded and that activity was diminished by LPS. In concert, these findings demonstrate that KC mRNA stability is regulated by LPS-induced alterations in activities that govern both deadenylation and degradation of the mRNA body. The effects of IL-10 on KC mRNA stability reflect antagonism of the response to LPS. The Journal of Immunology, 2003, 170: 6202–6208.

Although inflammation serves to protect the host against injury and infection, such responses are frequently the cause of substantial tissue damage and necessitate stringent regulatory control to minimize the detrimental effect. Although all cell types within an injured tissue participate in the inflammatory response, the process is orchestrated by infiltrating inflammatory leukocytes, particularly mononuclear phagocytes, and involves changes in the expression of multiple cytokine and chemokine genes (1–3). In the course of an inflammatory response, the expression of most cytokine and chemokine genes is mediated by dramatic changes in the frequency of transcriptional initiation (2). Posttranscriptional controls, however, are now believed to be important contributors as well. For example, genetic disruption of the posttranscriptional control of TNF-α expression results in dysregulated accumulation of this cytokine, leading to an overwhelming systemic inflammatory syndrome and death (4, 5). Indeed, modulation of mRNA decay has been shown to be an important regulatory feature controlling the expression of genes encoding cytokine and chemokine genes (6–11).

Alterations in gene expression involving either transcriptional or posttranscriptional mechanisms are the result of the response to a diverse spectrum of both pro-and anti-inflammatory agents encountered by leukocytes and other cell types within the injured tissue microenvironment. Components of the bacterial cell wall, including LPS, are potent stimuli of chemokine expression in a wide variety of cell types including macrophages, neutrophils, and endothelial cells through interaction with one or more Toll-like receptors (12–16). Anti-inflammatory regulation is provided by a variety of cytokines, such as IL-10, that act to suppress the expression of LPS-induced mRNAs (17, 18).

IL-10 signals through a type II cytokine receptor complex that results in the phosphorylation and dimerization of STAT3 (19, 20). Although this is believed to be necessary for IL-10-mediated anti-inflammatory action, it is apparently not sufficient (21, 22). IL-10 is also known to induce expression of the suppressor of cytokine signaling (SOCS)-3 and this appears to be an important feature of its inhibitory action (23).

LPS and IL-10 have been reported to achieve their differential effects on cytokine and chemokine gene expression through both transcriptional and posttranscriptional mechanisms (6, 7, 24–26). Although several previous reports suggest that LPS can promote stabilization of selected proinflammatory mRNAs (10, 27, 28), this has been somewhat difficult to demonstrate directly because such mRNAs are frequently undetectable in the absence of the primary stimulus. On the other hand, while IL-10 has been reported to suppress the activation of NF-κB and associated cytokine gene transcription (24, 29), it is also well documented to reduce the stability of several proinflammatory mRNAs (6, 7, 26, 30). The mechanisms required for the latter activity, however, remain largely unknown.

The mechanistic determinants of mRNA stability have been the subject of numerous studies over the last decade (31–33). AU-rich...
elements (AREs) found in the 3′-untranslated terminal repeats (UTRs) of many cytokine mRNAs are well known to direct rapid decay of such messages (33). Moreover, several recent reports have demonstrated that a subset of ARE-containing mRNAs may be targeted for stabilization in response to extracellular stimulation (8, 11, 34). The first step in mRNA decay appears to involve the removal of the poly(A) tail through the action of a poly(A)-specific ribonuclease and this is followed by degradation of the mRNA body (33, 35, 36). Studies using a recently developed cell-free system indicate that a large multisubunit complex of exonucleases termed the exosome may be responsible for 3′- to 5′-directed decay of the mRNA body in mammalian cells (37, 38). Although several RNA-binding proteins exhibiting precise specificity for ARE sequences have been identified, cloned, and functionally linked with altered decay of ARE-containing mRNAs, the mechanisms through which they promote enhanced decay are not known (39–43).

In the present study, we have begun to explore the processes through which LPS and IL-10 regulate the stability of the neutrophil chemoattractant CXC ligand 1 (KC) (murine growth-related oncogene-α) in opposite fashion, using both intact cells and a newly developed cell-free system. We demonstrate that LPS can promote the stability of KC mRNA in mouse macrophages in a time-dependent fashion. IL-10 appears to stimulate the decay of KC mRNA by antagonizing the ability of LPS to promote enhanced stability. The effects of LPS and IL-10 can be replicated in a cell-free mRNA decay system that uses extracts from RAW264.7 macrophages. The process of mRNA decay exhibits ARE dependence and involves modulation of deadenylation and degradation of the mRNA body.

Materials and Methods

Reagents

DMEM, Dulbecco’s PBS, and antibiotics were obtained from Central Cell Services, Lerner Research Institute (Cleveland, OH). Brewer’s thiglycolate (TG) broth was obtained from Difco Laboratories (Detroit, MI). FBS was purchased from Bio Whitthaker (Walkersville, MD). Maxiscript in vitro transcription kit, cap analog (7 meGpppG), and salmon sperm DNA were obtained from Ambion (Austin, TX). Recombinant mouse IL-10 was purchased from R&D Systems (Minneapolis, MN) and LPS, gentamicin sulfate (G418), actinomycin D (ActD), and protease inhibitor mixture were obtained from Ambion (Austin, TX). Recombinant mouse IL-10 was pur-

Preparation of RNA substrates and in vitro decay assays

Plasmids were linearized with XhoI (for nonadenylated substrate, wtARE) or with NsiI (for the polyadenylated substrates, wtAREAp and muAREAp) and in vitro transcribed in the presence of cap analog (7 meGpppG) to generate a 5′-capped RNA substrate internally labeled with 32P. The RNA was purified from a 6% polyacrylamide urea gel. The specific activity of the substrate was generally ∼0.2 × 106 cpm per μg. For the in vitro decay assay, 32P-labeled RNA (1 × 105 cpm) was incubated with S100 extract (15 μg protein) in a 25-μl solution containing 10 mM HEPES (pH 7.9), 50 mM KCl, 0.2 mM EDTA, 1 mM DTT, 15% glycerol, and a protease inhibitor mixture containing PMSF, pepstatin A, E-64, bestatin, leupeptin, and aprotinin. Protein concentration was measured according to the method of Bradford (46). The extracts were stored in aliquots at −80°C.

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Results

LPS stabilizes KC mRNA

We have previously demonstrated that IL-10 can increase the rate of KC mRNA decay and this effect depends upon AREs located within the 3′-UTR (6, 7). However, the mechanistic linkage be
tween IL-10 and the decay of targeted ARE-containing mRNAs remains unknown. Because LPS has been reported to stabilize
some ARE-containing cytokine mRNAs, we reasoned that the ability of IL-10 to promote increased mRNA degradation might represent a combination of two separate events: the LPS-mediated stabilization of KC mRNA and the antagonism of this response to LPS by IL-10. As a first step toward testing this hypothesis, the half-life of KC mRNA was determined in primary macrophages at different times after stimulation with LPS. TG-elicited macrophages were stimulated with LPS for 1–5 h and ActD was added to inhibit further transcription. After the indicated times, total RNA was isolated and used to determine KC mRNA levels by Northern blot hybridization (Fig. 1). The half-life of KC mRNA was <30 min when measured at 1 h after stimulation but was markedly increased (to >2 h) when determined after 2 h of LPS stimulation. This increase in half-life was a transient change and by 5 h had declined again to near the levels seen at 1 h. Hence, KC mRNA stability changes markedly over the time course of LPS stimulation.

**LPS and IL-10 modulate KC mRNA stability in opposite fashion**

To examine the effect of IL-10 on the acquisition of enhanced KC mRNA stability, elicited peritoneal macrophages were stimulated with LPS alone for 1 or 2 h or LPS along with IL-10 for 2 h before the addition of ActD to stop further transcription. Cultures were subsequently harvested immediately, 1, or 2 h later and total RNA was prepared and used to assess the percentage of remaining KC mRNA by Northern blot hybridization (Fig. 2). As seen in the experiment presented in Fig. 1, KC mRNA decayed rapidly in cells treated with LPS for 1 h but was at least four times more stable in cells that had been treated with LPS for 2 h ($t_{1/2} = 30$ min at 1 h and $>120$ min at 2 h). In cells cotreated with LPS and IL-10 for 2 h, the acquisition of enhanced stability was not observed. This suggests that IL-10 antagonized the stabilization response to LPS since the $t_{1/2}$ for KC mRNA was comparable in cells treated with LPS alone for 1 h and in cells treated with both LPS and IL-10 for 2 h.

Although these studies indicate that LPS treatment can stabilize KC mRNA, the half-life of the message in the absence of LPS stimulation cannot be determined in this experimental setting because expression itself is dependent upon LPS-stimulated transcription. To directly assess the effects of LPS on KC mRNA stability, we used a recently described model in which KC mRNA expression is controlled via a tetracycline-dependent promoter (42). A line of RAW264.7 cells was stably transfected to express the tetR-VP16 fusion protein in which transcription from a tetR promoter is terminated in the presence of tetracycline or its derivative Dox, allowing determination of the decay of specific mRNA without the use of transcriptional poison such as ActD. The parental strain of RAW264.7 cells used to create the stable tetR-VP16-transfected macrophages does not express the KC mRNA and thus allows detection of transfected full-length KC mRNA in the absence of endogenous gene background.

The tetR-VP16 RAW264.7 cells were transfected with a plasmid encoding the full-length KC mRNA under control of a TRE promoter (KCcDNA). Three hours posttransfection, the cells were divided into separate culture dishes for different treatment conditions. Eighteen hours later, the cells were treated or not with Dox (100 ng/ml) in the presence or absence of LPS (10 ng/ml) for 2 or 4 h. KC mRNA decayed rapidly in the presence of Dox but was more stable when LPS was added along with Dox (Fig. 3A). Expression of a control mRNA (luciferase) showed no decay following addition of Dox and no LPS sensitivity (Fig. 3B). The rapid decay of KC mRNA was dependent upon sequences present in the 3'-UTR since cells transfected with a plasmid encoding only the

**FIGURE 1.** LPS stabilizes KC mRNA. A, TG-elicited macrophages were treated with LPS (10 ng/ml) for the indicated times before the addition of ActD (5 
μg/ml) to block transcription. Individual cultures were harvested at the indicated times after ActD and used to prepare total RNA for determination of KC mRNA levels by Northern blot hybridization. B, Autoradiographs were quantified using the NIH Image software package. Levels of KC mRNA were normalized to those of GAPDH (data not shown) in each sample. Similar results were obtained in two separate experiments.

**FIGURE 2.** Decay of KC mRNA is regulated by LPS and IL-10. A, TG-elicited primary macrophages were stimulated with LPS (10 ng/ml) alone or with IL-10 (10 ng/ml) for the indicated times followed by treatment with ActD (5 
μg/ml). Cultures were harvested after 0, 1, or 2 h and total RNA was prepared and analyzed by Northern blot hybridization for KC mRNA levels. B, The autoradiographs were quantified for KC mRNA levels relative to GAPDH mRNA levels on the same blot (data not shown) using the NIH Image software package. Similar results were obtained in three separate experiments.
5'-UTR and coding region of KC mRNA (KCΔ3'UTR) exhibited higher expression levels which did not decline in the presence of Dox (Fig. 3C).

Consistent with the results from Fig. 2, IL-10 prevented the ability of LPS to stabilize transgenic KC mRNA decay. tet-off RAW264.7 cells transfected with pTRE KCcDNA showed rapid decay following addition of Dox that was delayed in the presence of LPS (Fig. 4A). This stabilization was lost in cells treated with Dox in the presence of both LPS and IL-10. This inhibitory effect of IL-10 was indirect because there was no difference in mRNA decay in cells treated with Dox in the presence or absence of IL-10 alone (Fig. 4B). This supports the hypothesis that the effect of IL-10 is to antagonize the stabilizing action of LPS.

Stimulus-dependent changes in mRNA stability are replicated in a cell-free mRNA degradation system

To further evaluate the mechanisms through which chemokine mRNA stability is controlled in response to extracellular stimuli, a cell-free system was used to study the degradation of the 3'-UTR fragment of KC mRNA in response to LPS and IL-10. A cell-free decay reaction was performed in the presence of S100 cell extract and poly(A) as indicated. The reaction products were resolved on a 6% polyacrylamide gel and analyzed by autoradiography. Loading control RNA in each sample and the position of the deadenylated substrate are also indicated. Similar results were obtained in three separate experiments.
FIGURE 6. LPS can modulate the degradation of both polyadenylated and nonadenylated substrates. A, The decay of the polyadenylated (wtAREpA) and nonadenylated (wtARE) substrates were compared by incubating the respective substrates with S100 extracts prepared from untreated (NT) or LPS-stimulated RAW264.7 cells. The cell-free decay reaction was at 30°C for the indicated time intervals. The reaction products in each case were resolved on a 6% polyacrylamide urea gel and analyzed by autoradiography. Loading control RNA in each sample is also indicated. Similar results were obtained in two separate experiments. B, The samples in A were quantified by determining the remaining TCA-insoluble radioactivity as described in Materials and Methods.

cell-free system of mRNA decay was used. Several recent reports have described a cell-free system that mimics some important features of mRNA decay in vivo (37, 38). RAW264.7 cells were used to prepare an S100 extract as described in Materials and Methods. 5' capped, polyadenylated (27As), and 32P-radiolabeled RNA substrate corresponding to a 120-nt sequence derived from the 3'-UTR of the KC mRNA (residues 379–502) was prepared by in vitro transcription. This sequence has been previously demonstrated to mediate rapid decay of KC mRNA in both macrophage and nonmacrophage cell lines (7, 9). In the presence of cell extract prepared from untreated RAW264.7 cells, this polyadenylated substrate mRNA was degraded over 30 min only upon addition of free poly(A) (Fig. 5A). The position of the deadenylated intermediate is indicated in Fig. 5. The modest accumulation of this product suggests that the process of degradation involves at least two steps: deadenylation followed by degradation of the mRNA body. The addition of free poly(A) is apparently required to compete with poly(A)-binding protein, which can protect polyadenylated mRNAs from exonuclease-mediated degradation. The free poly(A) dependence is a characteristic of some of the cell-free decay systems previously used to examine the mechanisms controlling the degradation of ARE-containing mRNAs (45).

To determine whether the decay of capped and polyadenylated substrate RNA in this cell-free system reflected the features of KC mRNA decay in macrophages, the sequence specificity and stimulus dependence of the activity was examined. Extracts from untreated cells demonstrated time-dependent decay over a 30-min incubation period (Fig. 5B). Although extracts prepared from LPS-treated macrophages had a markedly reduced capacity to promote degradation, extracts prepared from cells cotreated with LPS and IL-10 exhibited decay activity comparable to untreated cells demonstrating the antagonistic effect of IL-10 on the response to LPS. The altered decay activities of extracts from LPS- or LPS and IL-10-treated cells closely resemble the pattern of KC mRNA decay seen in intact cells treated under similar conditions, suggesting that the differential effects of extracellular stimulation on mRNA decay in vivo can be reproduced using this cell-free assay. In a second experiment, the same extracts were assayed using a radiolabeled substrate in which the ARE motifs were all mutated (Fig. 5C). This mutated substrate showed little or no decay with any of the three extracts, illustrating the sequence specificity of the decay process involved in the cell-free assay system.

To determine whether the effect of LPS was on the rate of deadenylation and/or on the rate at which the mRNA body was degraded, the activity in untreated or LPS-treated cell extracts was assayed with RNA substrates either with or without the 27-residue poly(A) tail. Extracts from untreated cells rapidly degraded the polyadenylated substrate (wtAREpA) and this was markedly reduced in extracts from macrophages treated with LPS for 2 h (Fig. 6). When the substrate used was missing the poly(A) tail but still contained the ARE motifs (wtARE), similar differential decay was observed using the extracts from untreated or LPS-stimulated cells.

Discussion

Stringent regulation of proinflammatory gene expression is required to provide both adequate protection against infection as well as to prevent unnecessary tissue damage. Posttranscriptional controls, particularly at the level of mRNA stability, are now recognized as important targets for the regulation of inflammatory gene expression by extracellular agents (6, 8–10). These may be especially important for mRNAs encoding cytokines and chemokines, which are often short-lived due to the presence of ARE motifs in their 3'-UTR segments. Experiments described above were designed to determine 1) whether LPS enhances the stability of the mouse KC mRNA, 2) whether IL-10 acts directly to destabilize KC mRNA or rather antagonizes the stabilization response to LPS, and 3) to begin to identify intracellular mRNA decay mechanisms targeted by these two extracellular agents. The results demonstrate (1) that LPS enhances KC mRNA stability in a time-dependent fashion, (2) that IL-10 does not affect the stability of KC mRNA directly in the absence of LPS but rather blocks the ability of LPS to promote increased stability, and (3) that LPS treatment
stabilizes short-lived KC mRNA by reducing the activity of a sequence-specific decay mechanism(s) that includes both deadenylation and degradation of the mRNA body.

LPS has been reported to promote mRNA stabilization for a subset of induced inflammatory mRNAs (10, 27, 47). Although cyclooxygenase 2, IL-6, and IFN-β may be stabilized in monocytes following LPS stimulation, several reports suggest that TNF-α, although highly unstable, is relatively insensitive to the stabilizing signal (27, 48). This may reflect functional heterogeneity of the regulatory sequences that control mRNA stability. Moreover, the measurement of inducible mRNA stability is inherently difficult because expression of these mRNAs frequently requires transcriptional initiation in response to LPS and hence their decay in the absence of stimulus cannot be readily measured. In the present study, we provide two distinct observations that support the ability of LPS to promote stabilization of the chemokine KC mRNA. First, KC mRNA stability varied with time after stimulation by LPS; 1 h after addition of LPS, the half-life for KC mRNA was <30 min while by 2 h of stimulation this was increased to > 2 h. The modulation of stability was, however, transient and 5 h after stimulation the decay rate had increased to that seen early following stimulation. Second, application of tetracycline-controlled KC gene transcription allowed the comparison of KC mRNA stability in the presence and absence of LPS. In this experimental setting, LPS treatment resulted in reduced KC mRNA decay without any effects on the rate of KC gene transcription.

Although IL-10 has been shown to increase the rate of mRNA decay for several cytokine mRNAs including that encoding KC (6, 7, 26, 30), the mechanisms involved in this response are poorly understood. Particularly, it is not known whether IL-10 can directly modulate the process of mRNA decay or, rather, interferes with the response to LPS. The present findings demonstrate that the effect of IL-10 on KC mRNA is primarily achieved through inhibiting the ability of LPS to promote enhanced stability for select mRNAs. Using the tetR system, it is clear that IL-10 does not alter the rate of KC mRNA decay in the absence of LPS. In previous work, we reported that IL-10 increased reporter mRNA decay in the absence of LPS (7). However, in these earlier experiments, the cells were assayed shortly after transfection and it is likely that plasmid DNA (containing CpG motifs) provided a stabilizing influence comparable to that of LPS via stimulation through Toll-like receptor 9 (49). It is noteworthy that previous reports have shown that the effects of IL-10 on KC expression occur relatively late in the response to LPS and that IL-10 is an effective inhibitor of LPS-induced gene expression even when added well after the LPS (6, 26). This is consistent with the hypothesis that IL-10 works to block the time-dependent stabilization of mRNA by LPS that only becomes evident after > 1 h of stimulation.

It has been recently shown that the capacity of IL-10 to antagonize LPS-induced responses in macrophages depends upon activation of SOCS3 (23). Although the specific molecular target of SOCS3 in LPS-stimulated cells remains unknown, it seems likely to interfere with early signaling events based upon other examples of SOCS-mediated control of the cytokine response (50). This mechanism of action would be consistent with the finding that IL-10 acts indirectly on mRNA decay mechanisms by interfering with response to LPS. In this regard, the overexpression of SOCS3 is able to mimic some aspects of IL-10 action, including posttranscriptional inhibition of TNF production (23).

The intracellular mechanisms that mediate selective mRNA decay are at present only partially understood. The ARE motifs that promote rapid mRNA turnover are known to be recognized by ARE-binding proteins although the mechanisms through which such interactions modulate the rate of decay have yet to be determined (41, 51–53). Early studies demonstrated that shortening of the poly(A) tail was the initiating step for mRNA decay (33, 35). Recently, a large, multisubunit complex termed the exosome has been reported to mediate degradation of deadenylated mRNAs from their exposed 3′ ends (37, 38). Both deadenylation and exosome-mediated mRNA decay show preference for ARE-containing substrates (38, 54).

In the present work, we have used a similar cell-free system using the postpolysomal fraction (S100) from RAW264.7 macrophage-like cell line to evaluate the molecular basis for changes in selective mRNA decay following treatment with LPS and IL-10. The degradation of a polyadenylated substrate mRNA was dependent upon the inclusion of free poly(A) in the reaction buffer, suggesting that the mechanism involves titration of poly(A)-binding protein, thus freeing the poly(A) tail of the RNA substrate for interaction with other components of the degradation machinery, primarily a poly(A)-specific ribonuclease. As in other reports, the decay activity obtained from resting cells showed a strong preference for RNA sequences containing ARE motifs. More importantly, the decay activity in the cell-free system accurately reflected the degradation of KC mRNA in intact cells; LPS treatment reduced decay and this effect was reversed by cotreatment with IL-10. This experimental system can thus serve as a useful model for identifying key control points in the RNA decay process.

In this regard, LPS-treated extracts also showed reduced decay activity when the substrate RNA lacked the poly(A) tail. The finding that LPS treatment changed decay rates for both poly(A)+ and poly(A)− substrates indicates that the effects are not limited to control of deadenylation. Rather, they suggest that exosome activity is also reduced in extracts from LPS-treated cells. This suggests that the molecular target of LPS is a feature shared by both processes. Because both deadenylation and exosome activity have been reported to show preference for ARE-containing substrates, the LPS-sensitive step is likely to involve modulation of ARE-dependent activities. Thus, emphasis in future work may be placed upon defining the ways in which ARE-binding protein expression and function vary in stimulated cells.

References
CONTROL OF CHEMOKINE mRNA STABILITY


